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DIFFERENCES BETWEEN RESPONDENTS AND NONRESPONDENTS IN A MORBIDITY SURVEY INVOLVING CLINICAL EXAMINATION

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WHEN samples from the general population have been invited for examination at research clinics in several recent studies in the United States, the response rates have ranged from 55 to 72 per cent.[11,24,29,32] Response rates as low as this make serious increases in the size of the confidence intervals that must be placed around any prevalence estimates emanating from these studies.[7] Furthermore, conclusions are jeopardized[3] as to association between a disease and any host or environmental factors that may be of interest. Because of these difficulties it is important to know as much as possible about those who are willing to participate and those who refuse. Such information may aid in the planning of future surveys and help raise response rates.

The problem of low response rates was brought to our attention rather sharply in the course of our studies on arthritis. From a sample of 798* individuals who were selected for a complete medical survey, only 60 per cent were successfully examined. Even though our study was not designed to elicit information about the characteristics of respondents and nonrespondents, certain useful information was available. From this information we can report on the differences and similarities between those who accepted the examination and those who refused. Our main aim in this paper, however, is to dramatize the need for studying the characteristics of respondents and nonrespondents and to emphasize the the need for incorporating some study of this problem at the beginning of every survey.

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*See footnote to Table I.

SUMMARY OF PERTINENT LITERATURE

The literature on this problem is not extensive, although the increasing number of reports indicates the growing awareness of its importance and the necessity for the collection of data basic to its solution. The available material divides itself conveniently into three segments, to wit, attitudes toward health and disease, sociologic characteristics, and medical care patterns.

Certain individuals seem to have an unrealistic perception of disease, associated with failure to accept health survey procedures from which they might well benefit. This may take the form of believing that a particular disease cannot be cured,[33] or that it is an act of fate, or a curse, or punishment for some real or imagined sin.[1,10,28,30] Such people may feel it futile to seek medical examination and treatment. In some cases religious belief, in particular Christian Science, may lead to refusal.[17,20] Along with this, one sometimes meets unrealistic attitudes about health. This is principally expressed as a belief that the individual is in good health despite the fact that no valid evidence of this is available. In one study,[17] this type of reasoning was given by 27 of the 115 persons studied who had failed to take advantage of a community x-ray survey. Contrary to this reasoning, evidence from many sources[15,23,27,32,33] indicates that disease is often found in individuals who thought themselves healthy.

Conscious or unconscious fear of illness may occasionally lead to the psychologic defense of denial, with consequent refusal to participate in surveys or examinations. In three studies[4,9,17] this was given as one of the important reasons for refusal to participate in x-ray programs, the subjects expressing fear of being sick and preferring not to find out about it.

Participation as a function of age and sex has been considered in almost every study on this subject and the results are not wholly consistent. With regard to age, it has been a consistent finding that older people are poor participants. Data from five surveys[2,8] indicate a decreasing rate of participation with increasing age, while data from other surveys[4,31] show low participation in the early twenties, followed by a rise in middle life, and then a steady decline after the age of 55. There is little evidence for any valid differences in participation rates by sex, for some studies have indicated that the greater proportion of nonparticipators were females,[2,8,13] others that males predominated in this respect.[2] One survey[4] noted that participation rates by sex were a function of age, with females having the higher rates under the age of 55 and males having higher rates in the older age groups.

Educational level has been consistently found to have some relation to participation rates. There is general agreement[13,14,17,18,21] that participation rates have a tendency to be higher in the better-educated groups than in the less well-educated ones. This appears to be independent of race and sex.[19]

Evidence from the literature about economic status and participation appears to be inconsistent. In two studies,[4,8] lower participation rates have been reported in x-ray surveys for those of higher economic status. One report[26] indicated no difference in the response rates of different economic groups in two x-ray surveys. In the polio vaccine trials, on the other hand, participation rates were higher among those in the higher economic groups.[14] It seems possible

that these conflicting reports may simply indicate that tuberculosis and poliomyelitis are not perceived in the same way by the several economic groups studied. Unfortunately no data are available on this point. Furthermore, some difference between economic groups in terms of reasons given has been noted.[17] For example, in 15 low-income families out of 100 families from all economic classifications, common reasons given were inconvenient time and inability to get out of the house. These reasons were not given by any of the nonparticipants in the above average income group.

The extent to which an individual participates in various community groups and the nature of these groups have shown some association with participation in the surveys. Thus, in the polio vaccine trials,[14] mothers of participants were more likely to spend two or more evenings a week in outside activities than were mothers of nonparticipants. Also, it was found[21] that attendance at P.T.A. meetings showed a positive association with correction of medical and dental defects discovered during medical examinations of school children.

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Two other social variables remain, ethnic group and occupational status. As to the former, it has been consistently noted that Negroes have higher response rates than whites. This phenomenon has been reported from Muscogee County, Georgia[4]; Cleveland, Ohio; Washington, D.C.; and Denver, Colorado.[2] With regard to occupation, lower participation rates have been observed among housewives, self-employed, and unemployed people than among regularly employed people.[13,31]

Data which relate to the medical care practices of the individual are also relevant. Some survey workers[8,22] have found that those under treatment or supervision for tuberculosis were, on the average, less willing to come for a chest x-ray. In addition, a recent medical examination or an x-ray were given as refusal reasons by subjects in studies by Burke[4] and Henderson.[17] Finally, Thompson[31] reported that hospitalization in the year preceding an x-ray survey was associated with a low participation rate.

No one of the factors brought out in the above material is sufficient by itself to explain nonparticipation in health programs. Perception of health and illness, beliefs and fears about disease, education, economic status, age, sex, race, occupation, group participation, and recent medical care all have some bearing on this problem. Furthermore, it would seem that different factors are important for different kinds of investigations and in different places.

METHODS

The Arsenal Health District of the city of Pittsburgh has provided a field laboratory for a number of studies based on an area sample of 3,000 households drawn in 1951.[5,6] Information about these households was obtained by two conventional household morbidity surveys, the second of which was conducted in the summer of 1952. A subsample was later selected, each member of which was to be interviewed and asked to come to the health center for a physical examination in connection with a study of arthritis. Sixty per cent of the named sample actually participated in the examination. The rest refused to do so, or were unavailable due to death or removal from the county.

It should be made clear that the original design of the study was for the investigation of arthritis, not the problem of nonresponse. However, when it became apparent that the problem of nonresponse had an important bearing on the interpretation of data relative to arthritis, our attention was turned to a study of the participator and nonparticipator. Analysis of the questionnaire data obtained in the individual interview and in the two household surveys indicated that we did have 33 items at hand that might contribute to a better understanding of the problem. Therefore, it is with these two groups, the examined and nonexamined, and information about them which was obtained from the 2 household surveys and the arthritis interview, that we are concerned in this paper.

Before proceeding to a description of the study sample and a discussion of certain statistical problems in the handling of the data, it is important to say something about the amount of effort expended and the techniques used in trying to persuade individuals to participate in the study. As mentioned above, each individual was interviewed personally, but was not informed at the time of interview that he would necessarily be examined, for it was planned to interview a sample larger than could be handled for the examinations and it was desirable to handle all interviews in a standard manner. Subsequently, each individual who was to be examined was approached again by one of the interviewers. At first this was done on the telephone, and those who did not accept then were, of course, visited in their homes; but often the interviewers would report that the pattern of refusal had been set on the telephone and they were unable to change this.

About halfway through the study, the policy was changed and all appointments for the clinic were made on the basis of personal contact by the interviewer. Surprisingly, the results were not much improved. However, other factors operated to obscure a possible improvement and we are still of the belief that a personal visit is more effective than a telephone call. When an individual was housebound, one of the study physicians would call at the house and make what examinations were possible. House calls were also made in certain selected cases where the interviewer felt that though she had been unsuccessful in persuading the individual to come to the health center, one of the doctors arriving at the house unannounced would be received.

Throughout the study the principal emphasis was on personal motivation. Occasionally the technique of third party selling was used but this was not easy when dealing with a scattered sample of an urban population. Relatively little use was made of newspapers, radio, or television, because these media had the potentiality of reaching all of the million and a half people in Allegheny County and many outsiders. In fact, on the two occasions when mass media were tried, the secretarial staff become overloaded with telephone calls from arthritics expressing a desire to be included in the study and letters were received from many parts of the United States. This experience indicated to us that it was necessary to focus sharply on the individuals concerned.

The characteristics of the persons doing the interviewing and making the appointments are, of course, important in any work of this sort. The bulk of

the appointments were made by 4 married women, all over 30 years of age. All but one had had previous interviewing experience and were all proficient in establishing relationships quickly. One of them was, in fact, so extraordinary in this respect that she received nearly 100 Christmas cards from friends that she made in the area while interviewing. This interviewer was also able to speak Polish, which helped in dealing with the many people of that nationality in the area. With regard to the persistence with which the subjects were pursued, it should be said that when an interviewer was prepared to give up pursuing a given individual for an appointment, the case was reviewed with the principal investigator who almost always was able to suggest some additional approach.

The staff will long remember the young couple who were followed through three changes of address with countless visits and telephone calls and a collective total of ten broken appointments. When the husband was finally "captured" unawares and brought in to the clinic without appointment, he was successfully examined. His wily wife, however, finally agreed to come without fail if we would also examine her mother who was not included in the study. Her mother came alone.

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It should be clear, however, that since there was intention to use this same sample for other purposes at a later date, efforts were avoided that were deemed likely to antagonize the individual if unsuccessful. The possibility of using the approach of Hansen and Hurwitz[16] was considered. This involves the selection of a subsample from the nonrespondents and the use of strenuous measures to obtain information from it. Some inference can then be made about similarities between the respondents and the nonrespondents. We felt, however, that we had already utilized every technique we knew so the idea was discarded.

We turn now to the structure of the sample (Table I). Here it is seen that the sample was divided into 6 strata, 3 for males and 3 for females, the stratification being based on response to questions relative to arthritis and rheumatism in the second household survey. Thus, if an individual was reported to have arthritis or rheumatism, he or she was placed in stratum one. If the response was "No" to the question on arthritis or rheumatism, but "Yes" to any question on a list of symptoms, then the individual was placed in stratum two. Finally, if the response was "No" to all of the pertinent questions, then the individual was placed in stratum three. As may be seen from Table I, males in strata one and two were sampled at a rate of 60 per cent while females from these strata were sampled at a rate of 30 per cent. For stratum three a 7 per cent sample was drawn.

This study then concerns those 478 persons who were examined and compares them with the 216 persons who refused examination. When we deal with certain material taken from the household survey, we have added to the nonparticipator group 35 cases who refused the individual interview, making a total of 251 who refused examination or interview.

When presenting estimates of the situation in the population as a whole, we have deemed it more reliable to deal only with appropriately weighted figures.

TABLE I. POPULATION NUMBERS, SAMPLE NUMBERS, AND RESPONSE CHARACTERISTICS BY SEX AND STRATUM FOR THE PITTSBURGH ARTHRITIS STUDY, 1952-1954

(Numbers in square brackets are per cent of sample)

(1) SEX	(2) STRATUM	(3) POPULATION SIZE	(4) SAMPLE SIZE	(5) EXAMINED	(6) REFUSED EXAM.	(7) REFUSED INTERVIEW	(8) UNAVAILABLE FOR EXAM.	(9) UNAVAILABLE FOR INTERVIEW
Both	All	7,132	798 [100]	478 [60]	216 [27]	35 [4]	18 [2]	51 [6]
M	All	3,436	408 [100]	237 [58]	110 [27]	19 [5]	12 [3]	30 [7]
A	1	182	108 [100]	74 [69]	19 [18]	5 [5]	0 [0]	10 [9]
L	2	143	84 [100]	51 [61]	28 [33]	3 [4]	0 [0]	2 [2]
E	3	3,111	216* [100]	112 [52]	63 [29]	11 [5]	12 [6]	18 [8]
F	All	3,696	390 [100]	241 [62]	106 [27]	16 [4]	6 [2]	21 [5]
E	1	357	108 [100]	72 [67]	26 [24]	4 [4]	0 [0]	6 [6]
M	2	203	60 [100]	41 [68]	13 [22]	1 [2]	2 [3]	3 [5]
A	3	3,136	222* [100]	128 [58]	67 [30]	11 [5]	4 [2]	12 [5]
L								
E								

*Persons in stratum 3 in the age group 15 to 34 were sampled at half the rate for the rest of the stratum and cards were duplicated to compensate.

The weights for each stratum are easily obtained. For example, the weight used for males, stratum one, is $\frac{182}{108} \times \frac{1,000}{7,132} = 0.236$. Such factors bring the population of reference to a total of 1,000 and the basic divisions of interest to us appear in the following proportions.

Examined	562
Refused Examination	290
Refused Interviews	48
Not Available	100
Total	1,000

RESULTS

The items available for study can be divided conveniently into those related to arthritis and other chronic illness, those related to the medical care patterns of the individual and his household, and certain social factors. Each division of items will be discussed in turn.

1. *Items Relating to Arthritis and Other Chronic Illness.*—The first information in this area comes from the response rates by stratum, as shown in Table II. It will be remembered that the strata were drawn according to answers given by the household respondent concerning rheumatism or arthritis and certain symptoms of these conditions. Clearly, the fact that the respondent believed that the individual in question had arthritis is to some extent related to his participation. This seems to be more marked for males than for females. Turning to item 1 in Table III we see the extent of the bias of the examined

TABLE II. PARTICIPATION RATES BY STRATUM FOR THE PITTSBURGH ARTHRITIS STUDY

	STRATUM		PER CENT OF TOTAL	PER CENT OF THOSE INTERVIEWED AND AVAILABLE
MALES	1	A or R*	69	80
	2	Symptoms	61	64
	3	Neither	52	64
FEMALES	1	A or R*	67	73
	2	Symptoms	68	75
	3	Neither	58	66

*Arthritis or rheumatism.

TABLE III. A COMPARISON OF THE PROPORTION OF RESPONDENTS AND NONRESPONDENTS GIVING AN INTERVIEW REPORT OF CERTAIN MEDICAL ITEMS

INTERVIEW REPORT OF	PROPORTION REPORTING AMONG		DIFFERENCE
	RESPONDENTS	NONRESPONDENTS	
1. Arthritis or rheumatism*	0.09	0.06	0.03
2. Arthritis or rheumatism	0.21	0.14	0.07
3. One or more rheumatic conditions	0.54	0.37	0.17
4. Joint pain	0.45	0.34	0.11
5. Morning stiffness	0.29	0.18	0.11
6. Joint swelling	0.18	0.13	0.05
7. History of joint trouble:			
<4 joints	0.24	0.22	0.02
>4 joints	0.25	0.14	0.11
8. Joint trouble now:			
<4 joints	0.17	0.08	0.09
>4 joints	0.06	0.02	0.04
9. Disability due to arthritis:			
moderate	0.13	0.10	0.03
marked	0.14	0.05	0.09
10. Joint injury	0.32	0.32	0.00
11. Other chronic disease*	0.11	0.09	0.02
12. Arthritis in household*	0.10	0.13	−0.03
13. Other chronic disease in household*	0.14	0.22	−0.08
14. Arthritis or rheumatism *and* morning stiffness *and* joint swelling	0.08	0.04	0.04
15. Arthritis or rheumatism *or* morning stiffness *or* joint swelling	0.44	0.27	0.17

*Data from household survey.

sample with regard to response on this question. Arthritis or rheumatism was reported on the household survey by 9 per cent of those who responded to urging to come for examination and by only 6 per cent of those who failed to respond. The next item is the response to the same question on the individual interview. The prevalence of positive responses to this question is somewhat higher and the difference between the proportions among respondents and nonrespondents is larger, but the ratio of the proportions is unchanged. Similar bias is seen for each item down through item 9. However, items 10 to 13 show no association with participation. At this point it is important to emphasize that there has been no selection of items for presentation in order to emphasize a point. Instead, all the items available have been reported. It is evident, then, that there is an appreciable bias in the direction of participation by people who report arthritis or some of its manifestations.

The last 2 items are of interest for they further confirm the above statement by showing that combinations of the items listed in the upper part of the table produce more striking evidence of bias than do the components individually. Item 14 should be noted particularly because it has been shown in an earlier report[25] that this set of 3 items is the most satisfactory interview index of rheumatoid arthritis. In this case the difference between the proportions is not large, but the proportion among respondents is double that among the nonrespondents. Another way of stating this is to say that 81 per cent of persons giving positive answers to these three items responded to the invitation to come for examination. Item 15 also shows a striking difference between the proportions.

2. *Items Relating to Medical Care.*—The available items in this area are listed in Table IV. Here it is noted that, though no single one of the items is particularly striking, there is a rather marked bias in favor of participation by persons with positive answers on any two of these items.

TABLE IV. A COMPARISON OF THE PROPORTION OF RESPONDENTS AND NONRESPONDENTS GIVING AN INTERVIEW REPORT OF CERTAIN MEDICAL CARE ITEMS

INTERVIEW REPORT OF	PROPORTION REPORTING AMONG		DIFFERENCE
	RESPONDENTS	NONRESPONDENTS	
1. Three or more hospitalizations in the past 5 years	0.03	0.01	0.02
2. Two or more doctors seen in past year*	0.10	0.04	0.06
3. Family doctor named*	0.93	0.85	0.08
4. Participation in x-ray survey	0.64	0.57	0.07
5. Two or more of the above items	0.37	0.22	0.15

*Data from household survey.

3. *Social Factors.*—The fact that age has a minor influence on response and sex little, if any, influence is shown in Fig. 1. It is evident however that males over 55 years of age were rather resistant to efforts to persuade them to come for examination.

In Table V, which contains social items, there are only 2 factors which stand out clearly. The first is that those people who name specific problems, when asked what they worry about, have a considerably greater probability of being respondents than do those who claim that nothing ever bothers them. The second

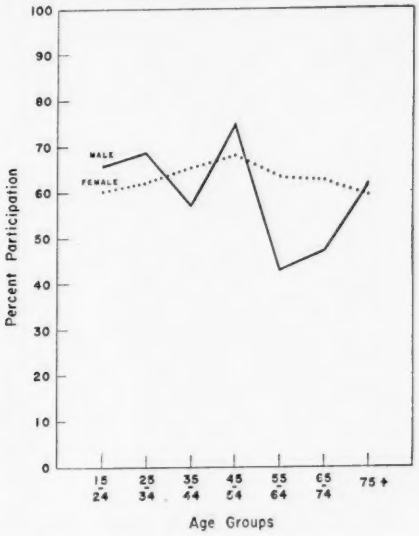

Fig. 1.—The per cent of participation in the arthritis examination by age and sex.

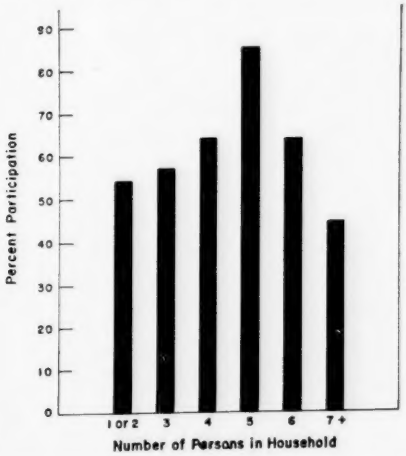

Fig. 2.—The relationship between household size and paticipation in the Pittsburgh Arthritis Study.

outstanding item is size of household, item 14. Further information on this subject is presented in Fig. 2 where it is shown that persons living in households containing 5 persons were much more likely to accept the examination than were those in larger or smaller households. The explanation for this is not clear. However, we can state that this finding is not secondary to variations in age,

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marital status, or extent of medical care. Furthermore, it is true for both sexes but is more striking for females. When the 2 factors of specific worries and family size are combined in item 16, one notes that the proportion with these characterics among respondents is two and one-half times as great as among nonrespondents.

TABLE V. A COMPARISON OF THE PROPORTION OF RESPONDENTS AND NONRESPONDENTS GIVING AN INTERVIEW REPORT OF CERTAIN SOCIAL ITEMS

INTERVIEW REPORT OF	PROPORTION REPORTING AMONG		DIFFERENCE
	RESPONDENTS	NONRESPONDENTS	
1. Age under 55	0.76	0.67	0.09
2. Marriage	0.69	0.70	−0.01
3. Place of birth: Allegheny County	0.75	0.73	0.02
U. S. other than Allegheny County	0.12	0.15	−0.03
outside U. S.	0.13	0.12	0.01
4. Occupation professional, managerial, or sales	0.25	0.20	0.05
5. Education: less than eighth grade	0.21	0.16	0.05
eighth or ninth grade	0.24	0.31	−0.07
more than ninth grade	0.55	0.53	0.02
6. Family Income: <$3,000	0.35	0.38	−0.03
$3,000–$4,449	0.38	0.40	−0.02
>$4,500	0.27	0.22	0.05
7. Leisure Activities: Age 20 to 29			
no free time	0.13	0.12	0.01
passive or inactive	0.31	0.33	−0.02
active or very active	0.56	0.55	0.01
8. Average amount of worry	0.52	0.41	0.11
9. Specific worries	0.75	0.54	0.21
10. Two or more organization memberships	0.21	0.14	0.07
11. Interest in service oriented organizations	0.24	0.26	−0.02
12. Signature	0.94	0.84	0.10
13. Interview duration 15 minutes or more	0.66	0.56	0.10
14. Size of Household: 1 to 3	0.37	0.48	−0.11
4 to 5	0.45	0.27	0.18
6 to 8	0.18	0.25	−0.07
15. Socioeconomic status:			
(1) + Lowest	0.16	0.17	−0.01
(2)	0.44	0.48	−0.04
(3)	0.28	0.27	0.01
(4) + Highest	0.12	0.08	0.04
16. Specific worries and family size 4 to 6	0.44	0.18	0.26

Signature and interview duration (items 12 and 13) are two further items deserving comment. With respect to the interview duration, it seemed likely that those who gave an interview only under protest would do so rapidly and would be unlikely to come for examination. The slight association between long interviews and response for examination suggests that this is in fact true. With respect to signature we have a very interesting situation. Each subject was asked to sign a permission form allowing access to his or her past medical records. Ninety-one per cent of those interviewed signed this form. Among the males, who refused to sign this form, there was almost complete lack of response for the examination. This was not true for the females.

Finally the important items of occupation, education, and income must be examined. In doing this it is noted that the upper and lower educational groups are found in excess among the participants, while those whose education ended at the junior high school level are found in excess among the nonparticipants. This odd finding suggests that further study of the attitudes of persons of intermediate educational achievement might lead to new ideas about this response problem. Next, though family income does not show a striking overall effect, its influence on those under 45 years of age is quite marked as shown in the following.

Annual Family Income	Per Cent Participation
<$1,500	59
$1,500–2,999	65
$3,000–4,499	73
$4,500+	81

When these three items—occupation, education, and income—are grouped to form a rough index of socioeconomic status, we find that the proportional distributions are somewhat more striking. In fact, among those persons 15 to 44 years of age in the top socioeconomic group (about 8 per cent of the population of that age) 88 per cent responded for the examination. If such rates could be attained throughout the population, we would have no serious problem.

DISCUSSION AND RECOMMENDATIONS

From the above data, we can list some of the characteristics of the participator. He is apt to be able to specify his worries. He comes from a household of average or slightly above average size. As might be expected, persons with manifestations of chronic rheumatic disease such as joint pain, swelling, or morning stiffness are more likely to participate than those who are free of these complaints. The habit of making use of medical care facilities or exposure to them by virtue of necessity seems to favor participation. Generally speaking, income and socioeconomic status are not of great over-all importance; however, those with high status who are under 45 years of age have the highest participation rate of any group of appreciable size that has been studied.

Though we have been able to paint something of a picture of the participator or rather to suggest among what groups he is likely to be found, the nonparticipator has turned out to be more elusive. There seem to be only 2 small groups of those studied that have strikingly low participation rates. The first is the group of persons who live in households of 8 or more. Here the participation rate is down to 24 per cent. The lowest participation rate observed is 16 per cent. This occurred in the small group of males who refused to sign the slip giving permission for the staff to examine their past medical records.

The implications of low response rates in studies for the estimation of prevalence are serious. This is especially true when, as has happened in our study, there are differences in response rates between those who think they are affected by the disease in question and those who think they are free of it. Our method of dealing with this problem will be discussed in a forthcoming report on the prevalence of rheumatoid arthritis. As mentioned above, Berkson[3] has pointed

out the serious danger of drawing conclusions about associations where there may be differential response rates in the various cells of the table under consideration. Our thinking on this subject has been incorporated in an earlier paper.[25]

Summing up at this point, we have reviewed the literature on factors in participation, described our own experiences, and presented data on a field study involving medical examination. Based on this material we now propose to make certain recommendations for those who are planning new studies. These are based more on our experience than on the results of the analyses. This is understandable in view of the fact that the study was not designed originally to investigate the nonresponse problem.

We have 4 recommendations. First comes persistence. Though there is little on this subject in the literature, perhaps because it is a quality hard to measure, the evidence of its importance is best borne out by the fact that it always comes up when survey people get together. The questions such as "How long did you keep at it?" "What kind of tricks did you try?" "How much did you budget for the selling aspects of the study?" are hard questions for any of us to answer. Even the last is difficult to answer, for many of the people who do the persuading have other necessary functions in the organization and the estimation of time spent persuading a person to participate is at best a matter of judgment.

Second, we are convinced that the employment of what we refer to as high caliber people to do the job makes a very great difference in the success of the enterprise. This is, of course, true in all fields. The tendency in some quarters has been to use "cheap labor" for this purpose. As time goes on it is hoped that the skilled interviewer will become a more valued member of the field research team. The ability to relate to people is properly paramount among the skills required of a good persuader. In addition, he or she must have integrity and a certain bulldoglike unwillingness to give up.

The third important recommendation is in regard to the selection of the community for study. Present indications are that surveys in smaller communities tend to have higher response rates. The best evidence for this is the fact that the Framingham Heart Study[11] and the Hunterdon County Chronic Illness Study[32] had participation rates which were appreciably higher than those obtained in the Baltimore Chronic Illness Study[24] or the Pittsburgh studies of arthritis and heart disease.[29] We think that one of the reasons for this is that mass media can be more effectively used in a small town without running into the difficulty that was encountered by glaucoma screening in Cleveland,[12] where the response completely overwhelmed the available staff. Moreover, the use of a small community is likely to be accompanied by high sampling rates. When such is the case, third party selling becomes an important factor in the acceptance of the program. In urban areas with low sampling rates, the probability that members of the sample will be acquainted with one another is so low as to be of very little help.

Next to size of community, it is important to consider the medical habits, programs, and plans of the community. If these are sound, well accepted, and operated by skilled physicians, the probability of success is enhanced. A third point about selecting a community is that one is most successful in studying a

problem that the particular community recognizes as important. Thus, the performance of a field study on request is much more likely to meet with high response rates than when a community is selected by the investigator. Or to put it another way, it may be necessary to demonstrate the importance of a problem to a community before undertaking a study there.

Our fourth recommendation is that every new field study should have included, right from the start, at least a small study of the nonresponse problem. This will benefit not only the project by giving some idea of the characterics of those who would not respond, but will also benefit other survey students by giving new clues as to better approaches.

Finally, a number of minor points should be listed.

1. There is evidence that worriers participate more than those who have no specific worries. It seems reasonable to suppose, then, that a moderate amount of "scare propaganda" is appropriate for motivation. This suggestion is made despite the fact that a small number of people will always react to fear of illness with denial and refusal to participate, because they might discover they were not as well as they thought.

2. Special attention should be given to older people and people living in large households, for it is clear that they have low participation rates.

3. One should rely on personal contact rather than the telephone.

4. Greater use should be made of home examinations. A decision to go to the person rather than having the person come to the clinic should be made at the first sign of resistance, for some information is better than none.

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SUMMARY AND CONCLUSION

1. A detailed examination of the differences between those who accepted a medical examination in a study of arthritis and those who refused has been made.

2. Of 33 items examined, the following showed reasonable evidence of association with participation: (a) an interview report of arthritis or manifestations thereof; (b) interview evidence of utilization of medical services; (c) an ability to specify personal worries; (d) high socioeconomic status among young persons, but not among older people; and (e) residence in a household of five persons.

3. Based on our experience, we make certain recommendations for methods to be used in future studies. The most important of these is that a study of the nonresponse problem be built into each new field investigation as it is planned.

We are indebted to Joseph Rosenbaum and Theodore Rubin for guidance and assistance in the analytic work. We also wish to acknowledge the invaluable services of Ida Sissman, who served as Public Relations Consultant, and Eleanore Gill, who supervised the field staff.

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THE MELANOCYTIC (PIGMENTED) NEVUS

A Discussion of Its Management

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THERE has never been unanimity of opinion regarding the management of those lesions of the skin that are commonly referred to as moles or pigmented nevi.

It is the purpose of this presentation to list some general principles by which the practitioner may be guided in the selection of those lesions requiring prophylactic removal and the appropriate method of treatment.

Heretofore, the chief pitfalls in the development of a concerted point of view regarding the handling of these lesions were a lack of knowledge of their pathogenesis, the absence of a proper correlation of their protean clinical and histologic types, and the failure to elucidate their role as precursors of malignant melanoma. However, the last two decades have witnessed an impressive accumulation of knowledge in these areas,[1] enabling one to adopt some rules for a prophylactic approach which appear to have at least tentative validity.

I have proposed that these lesions be designated as melanocytic nevi.[2] The reason for offering a new term is an attempt to clear up some of the confusion that exists among clinicians regarding the pathology of these lesions and their proper nosologic status. The basic cellular element in these nevi is the melanocyte, the cell that elaborates the pigment melanin. While pigmentation is usually present in the melanocytic nevus, its absence is not rare when its constituent melanocytes are functionally inactive in so far as melanogenesis is concerned. Here, the term pigmented nevus would obviously be inappropriate. On the other hand, many other nevic lesions of nonmelanocytic origin, as well as some nonnevic lesions, may be incidentally pigmented. Table I illustrates how broad is the pathologic base giving rise to pigmented noninflammatory lesions and how poor a criterion pigmentation is when used alone for the diagnosis of a nevus of melanocytic origin. It is obvious that the term pigmented nevus can be only misleading. To pursue the matter further, the term "mole" is often loosely

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used to include elevated pigmented lesions of diverse cellular origin. It would seem to me that the designation "melanocytic nevus" is pathologically correct and, therefore, would help to clear up some of the misunderstandings discussed above. The differential diagnosis of the melanocytic nevus is discussed elsewhere.[3]

TABLE I. PIGMENTED LESIONS OF THE SKIN*

NEVOID			NONNEVOID
MELANOCYTIC	NONMELANOCYTIC	MIXED	
Junction nevus	Verruca seborrheica	Nevus pigmentosus et pilosus (melanocytic and follicular elements)	Pigmented epithelioma
Compound nevus	Epithelial nevus		Sclerosing hemangioma
Juvenile melanoma	Pigmented tag	Nevus pigmentosus et vasculosus (melanocytic and vascular elements)	Senile keratosis
Intradermal nevus	Trichoepithelioma		Kaposi's sarcoma
Lentigo	Vascular nevus	Nevus verrucosus (melanocytic and epithelial elements)	Glomus tumor
Blue nevus	Ephelis (freckle)		Accessary nipple

From Shaffer, B.: Identification of Malignant Potentialities of Melanocytic (Pigmented) Nevus, J.A.M.A. **161**:1222, 1956.

*These lists are not complete but give important examples.

There is cogent evidence to indicate that the pigment-forming cell, the melanocyte, originates in early embryonic life in the primitive neural crest and in man wanders out to its normal site at the epidermodermal junction to produce normal pigmentation of the skin* (Table II). Certain foci of these cells (at varying times postnatally but usually within the first three decades) undergo proliferative changes designated as junctional activity because of their location at the epidermodermal junction; but, as the process continues, the involved melanocytes separate from the epidermodermal junction to form bands and clumps of cells entirely within the corium. In their final stages many of these cells involute and subsequently are replaced by a fibrillary substance resembling a schwannoma. There are, therefore, many histologic stages of these junctionally derived melanocytic nevi and these are reflected in various clinical appearances. Those nevi of this evolutionary line in which junctional activity is the sole histologic feature are the early or the immature forms (the junction nevus), while those in which this feature is no longer present are obviously the older or mature lesions (the intradermal nevus). It is quite apparent, however, that many transitional stages are to be found and these are designated as the compound nevus and the juvenile melanoma. Lesions in this evolving sequence

*Melanocytic activity in sites other than the skin such as the uveal tract of the eye, mucous membranes, and pia mater of the central nervous system will not be discussed here.

TABLE II. VARIETIES OF MELANOCYTIC NEVI

(All derived from melanocytes originating in neural crest in embryonic life)

JUNCTIONAL DERIVATION (HUES USUALLY YELLOWS, REDS, BROWNS, AND DARK BROWNS)	DERMAL DERIVATION (HUES USUALLY SLATE-BLUE)
Junction (immature) nevus*	
Compound (intermediate) nevus*	Blue nevus of Jadasshon
Juvenile melanoma*	Mongolian spot
Intradermal (mature) nevus	Nevus of Ota
Lentigo (inactive junction) nevus	

*Lesions with junctional activity. The lentigo may have potentialities for junctional activity.

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constitute the vast majority of melanocytic nevi. It is only in this series that junctional activity may be found and, with rare exceptions, it is only those lesions with junctional activity that possess the malignant potentialities in so far as melanoma is concerned. The quest for premalignancy, therefore, centers about the problem of detecting junctional activity in lesions of this group.

There is another much less common class of cutaneous melanocytic nevi which are derived from ectopic foci of melanocytes, appearing as original depositions within the corium (in contrast to their usual position at the epidermodermal junction). These might be described as dermally derived melanocytic nevi and their clinical types have been designated by various names, such as blue nevus of Jadassohn, Mongolian spot, and the nevus of Ota. Since none of these at any time has junctional activity, they are not ordinarly premalignant lesions and, indeed, melanoma derived from this group is exceedingly rare. Because of certain cutaneous optical characteristics, the colors of pigmented materials within the skin shift toward the blue end of the spectrum when these are deeply placed. Therefore, dermally derived melanocytic nevi are characterized by a dusky or deep blue, slaty color in contrast to the true hues of melanin, namely yellows, reds, and dark browns as predominantly seen in junctionally derived nevi where at least some of the pigment is usually quite superficial.

It is now recognized that most melanomas arise from the skin in two ways: (1) denovo, beginning either in presumably normal skin, or as a pigmented spot clinically known as lentigo maligna (or melanotic freckle of Hutchinson)[4] (these presumably account for about 35 to 75 per cent of melanocytic malignancies[5,6]); or (2) in a melanocytic nevus of junctional derivation with junctional activity.

The lentigo maligna is not a nevus at all, but a true malignant lesion from its very incipiency. It must, therefore, be carefully differentiated from the melanocytic nevus. Some of these differential features follow.

1. The onset of lentigo maligna is usually in the later decades, especially after the age of 50. Most melanocytic nevi appear in the first three decades and usually before the twentieth year.

2. There is progressive lateral spread of lentigo, usually sporadic, often very slow, but at times rapid and commonly progressing over a period of years. By contrast, the lateral growth of melanocytic nevi is exceedingly slow, usually in the early decades, upward and outward to form an elevated mass.

3. In the lentigo maligna, growth is often associated with a diffuse and ill-defined pigment infiltration into the presumably normal surrounding skin (pigment satellosis). This never occurs in melanocytic nevi. The periphery of a halo nevus (to be described below) is an inherent part of the melanocytic cellular structure and should not be mistaken for infiltration of pigment.

4. The pigment in lentigo maligna varies considerably in hue and density from time to time or even at the same time in different parts of the same lesion, and it often takes on a bluish to a slaty color similar to that seen in the dermally derived melanocytic nevi (the latter, however, do not show the other features listed here).

5. There may be, at times, a pearly translucency in the border of the lesion or within its substance, simulating that seen in a pigmented basal cell epithelioma. This may be rarely seen in a compound melanocytic nevus.

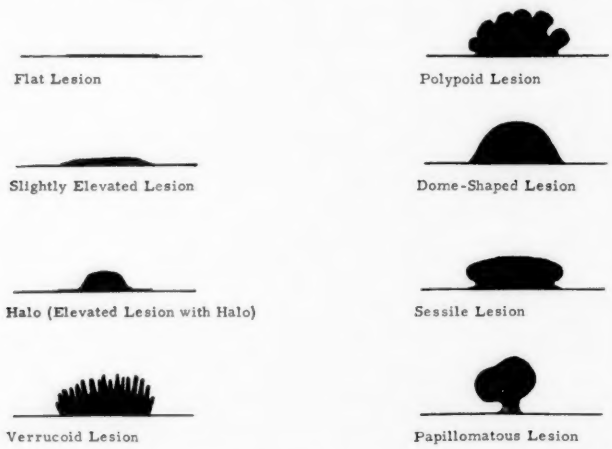

Fig. 1.—Diagrammatic representation in cross section of surface characteristics of morphologic types of melanocytic nevi. (From Shaffer, B., A.M.A. Arch. Dermat. 72:120, 1955.)

6. There may be a difference in degree of thickness and irregularity in the surface of the lesion, often associated with a mottling irregularity of its pigmentation. This is coarser and more "topographic" than that seen in verrucoid and polypoid melanocytic nevi.

7. There may be seen, also, superficial bleeding, inflammation, and ulceration.

8. Metastatic malignancy may appear almost from its beginning or, more commonly, it may remain as a malignancy in situ (often intraepidermal with pagetoid features) for many years.

In diagnosing the melanocytic nevus with junctional activity, the problem, then, is (1) to rule out nonmelanocytic lesions which, because of incidental pigment, may simulate the melanocytic nevus (Table I); (2) to exclude from among

the melanocytic nevi those of dermal derivation; and, finally (Table II), (3) to choose from among the numerous clinical varieties of the melanocytic lesions of epidermodermal derivation those lesions that have junctional activity.

Several facts of clinical importance seem to have emerged from a study of the clinicopathologic correlation of over 200 melanocytic nevi of epidermodermal derivation. I have discussed this in detail elsewhere.[2] A subsequent experience now amounting to approximately 100 nevi specimens has continued to substantiate these conclusions and to strengthen my conviction that the clinical evaluation of a melanocytic nevus can often be a useful guide in predicting the presence or absence of junctional activity.

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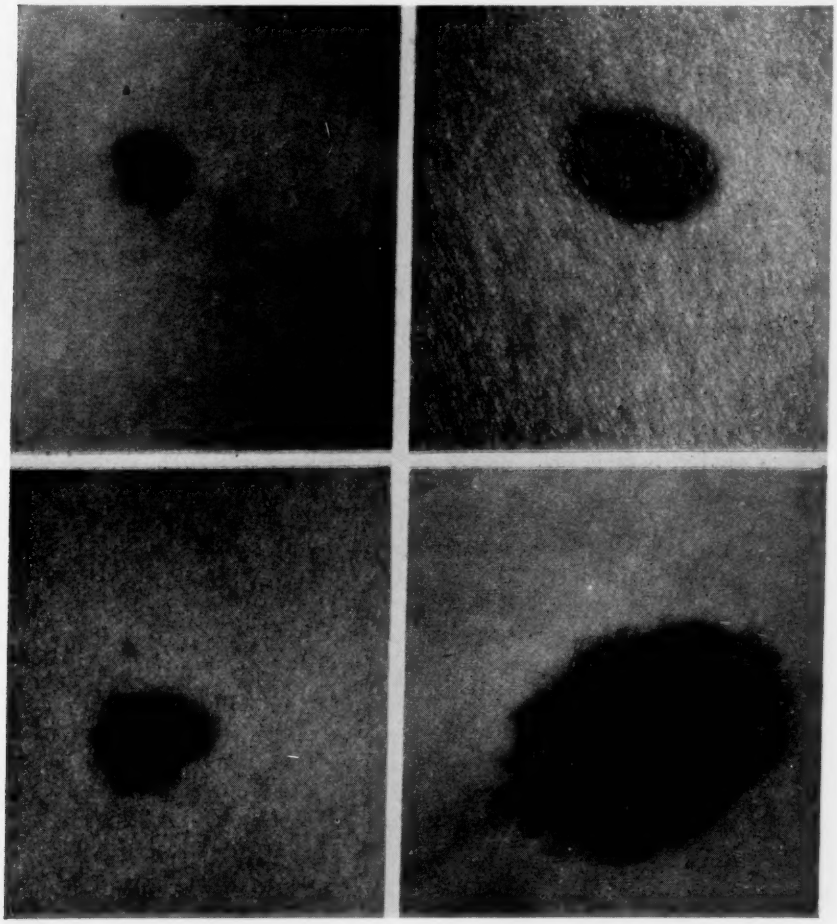

Fig. 2.—Morphologic types of pigmented (melanocytic) nevi. Black and white reproductions of Kodachrome transparencies. Upper left, Flat lesion: histologically a melanocytic junction nevus, note irregular somewhat hazy border and speckling of the pigment. Upper right, Slightly elevated lesion; histologically a melanocytic compound nevus. Lower left, Halo, an elevated lesion surrounded by a pigmented flat margin; histologically a melanocytic compound nevus. Lower right, Verrucoid lesion; histologically an intradermal melanocytic nevus with features of junctional activity. (From Shaffer, B.: Pigmented Nevi; A Clinical Appraisal in the Light of Present-Day Histopathologic Concepts, A.M.A. Arch. Dermat. 72:120, 1955.)

It was found that the morphology of the individual melanocytic nevus is the best single clinical index for diagnosing junctional activity. For this purpose melanocytic nevi of epidermodermal derivation were divided into various categories as shown in the following.

Flat lesions: These are pigmented spots without perceptible elevation or thickness. The pigment may be evenly distributed throughout the lesion in which case the lesion is designated as a "plain flat lesion," or it may have a speckled or mottled appearance often with an angular, irregular, or fuzzy border. In this case the lesion is called a "speckled flat lesion."

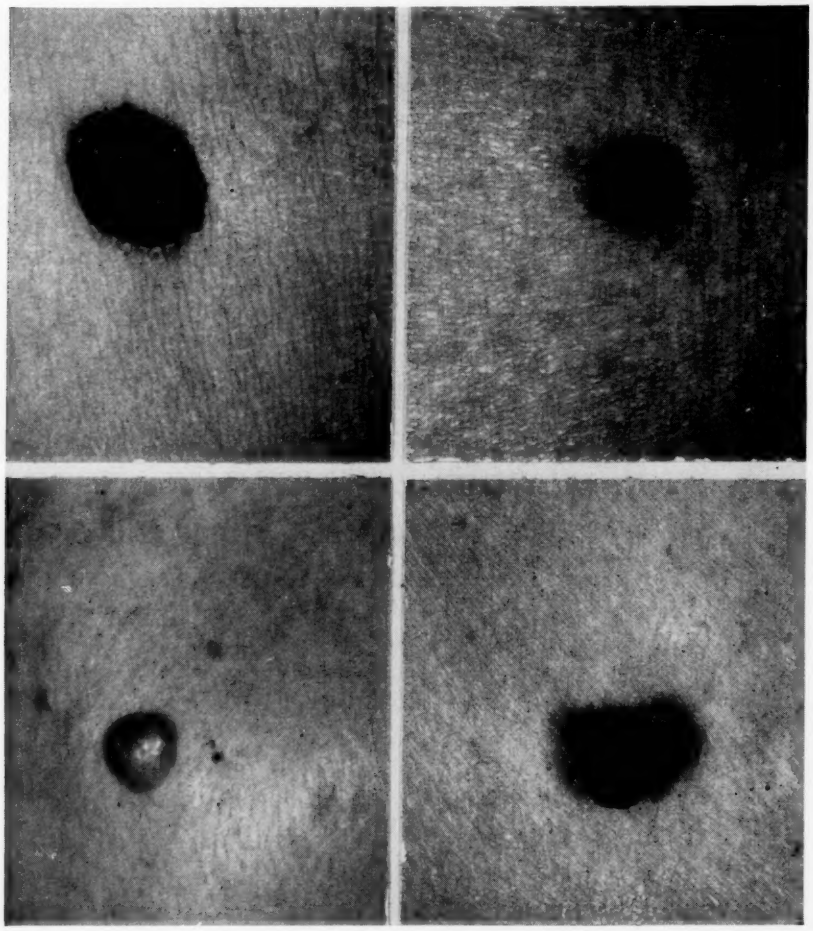

Fig. 3.—Morphologic types of pigmented (Melanocytic) nevi. Black and white reproductions of Kodachrome transparencies. Upper left, Polypoid lesion; histologically an intradermal nevus. Upper right, Sessile lesion; histologically an intradermal nevus. Lower left, Dome-shaped lesion; histologically an intradermal nevus. Lower right, Pedunculated lesion; histologically an intradermal nevus. (From Shaffer, B.: Pigmented Nevi; A Clinical Appraisal in the Light of Present-Day Histolopathologic Concepts, A.M.A. Arch. Dermat. 72:120, 1955.)

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Slightly elevated lesions: These have a just perceptible thickness or elevation.

Halo lesions: These are elevated lesions surrounded by a flat pigmented ring.

Verrucoid lesions: These are lesions the surface of which is covered by fine, digitate excrescences.

Polypoid lesions: These consist of grouped club-shaped or blunt protuberances.

Dome-shaped lesions: These are smooth elevated lesions.

Sessile lesions: These are elevated lesions with a slightly constricted base.

Pedunculated lesions: These are attached to the skin by means of a stalk or pedicle.

When these morphologic characteristics were combined with other clinical features the following clinicopathologic rules were found to have a high degree of reliability:

1. Plain flat melanocytic nevi occurring in the first three decades of life, and speckled flat nevi, slightly elevated nevi, halo nevi, and verrucoid nevi in all age groups are apt to show junctional activity.

2. Plain flat nevi in persons aged 30 and above, and all polypoid nevi, dome-shaped nevi, sessile, and pedunculated nevi are apt to be free of junctional activity.

3. Junctional activity diminishes with age and this applies to a certain extent for most morphologic types.

4. As one descends the cephalocaudal axis, i.e., as one goes from the head and the neck toward the anogenital regions and the hands, and feet, junctional activity becomes more likely for a given age group and for a particular lesion type.*

It follows that the older, more mature types of nevi (group 2) appear on the head and neck in the earlier decades of life and that the earlier, less mature types (group 1) commonly persist into the later decades on the distal segments of the extremities (especially the hands and feet), and the anogenital region. Lesions on the trunk are apt to occupy an intermediate status.

5. Crops of flat pigmented lesions appearing rather suddenly in preadolescence or early postadolescence are apt to be junctional in type.

6. All other things being equal, the older a particular lesion is and the earlier its onset in life, the less likelihood there is of junctional activity. This, in general, is a less reliable criterion than the others.

A classification giving the probability of junctional activity based on a combined consideration of morphology, age of patient, and distribution of these lesions is shown in Table III.

1. Junctional activity is almost certainly absent in polypoid, pedunculated, and sessile lesions irrespective of age or location. This also applies to dome-shaped lesions on the head, face, and neck in postpuberal period.

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*Apropos of this, Becker and Zimmerman[7] in a study of Negro fetuses found that the melanocyte first appeared on the head at the third month while it could not be detected until the fourth month on the caudal parts of the body.

TABLE III. EVALUATION OF JUNCTIONAL ACTIVITY IN MELANOCYTIC NEVI OF EPIDERMODERMAL DERIVATION

JUNCTIONAL ACTIVITY	MORPHOLOGIC TYPES	AGE GROUPS	LOCATION - SKIN SITES
Absent — almost certainly	Polypoid	All	All
	Pedunculated	All	All
	Sessile	All	All
	Dome	Postpuberal	Head, face, and neck
Absent — probably	Dome	Prepuberal	All
	Dome*	Postpuberal	Trunk, extremities, and anogenitalia
	Plain flat	30 years	All except hands, feet, and anogenitalia
Present — probably	Plain flat	30 years	Hands, feet, and anogenitalia
	Plain flat	0-30 years	All
	Slightly elevated	Postpuberal	All
	Verrucoid	Postpuberal	All
	Halo	Postpuberal	All
Present — almost certainly	Speckled flat	All	All
	Slightly elevated	Prepuberal	All
	Verrucoid	Prepuberal	All
	Halo	Prepuberal	All

*Inflammation and rapid growth may indicate junctional activity.

2. Junctional activity is probably absent in dome-shaped lesions in any location in the prepuberal period (providing these lesions are not inflammatory or undergoing rapid growth)* and also in the postpuberal period when found on the trunk, extremities, and anogenitalia. Plain flat lesions in persons above the age of 30, except those on the hands, feet, and anogenitalia, also belong in this category.

3. Junctional activity is probably present in plain flat lesions in the first three decades of life and at all ages when on the hands, feet, and anogenitalia. Slightly elevated, verrucoid, and halo lesions in postpuberty are also frequently the sites of junctional features.

4. Junctional activity is almost certainly present in flat speckled lesions in all age groups and at all sites. In this category belong also slightly elevated, halo, and verrucoid lesions in prepuberty as well as dome-shaped lesions in the prepuberal period with rapid growth and inflammatory features (often juvenile melanoma).

It is obvious that those lesions falling in group 1 need not be removed prophylactically and the indications for the prophylactic removal of those lesions in group 2 debatable. Lesions falling in groups 3 and 4 might be removed because junctional activity is often considered to be a justifiable indication for such action. However, it must be recalled that only 1 out of approximately 1,000,000

*The latter signs would indicate the probability of a juvenile melanoma or early malignancy. The juvenile melanoma is a lesion with greatly accentuated junctional activity so that it resembles histologically a true melanoma. It eventuates, however, into a mature, intradermal, nonmalignant melanocytic nevus. Dr. S. Wm. Becker, Sr., prefers to call these lesions juvenile pseudomelanomas. (Personal communication.)

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melanocytic nevi become malignant and many patients have as many as twenty or more such lesions on their skin.[8] Also, it must be realized that melanoma is a great rarity in preadolescence when junctional activity is most often present. It is quite apparent that the wholesale removal of these lesions is very often an impractical procedure. In the case of the adult there is debatable indication for the prophylactic removal of all lesions showing clinical evidences of junctional activity, but probably only those lesions on the hands, feet, and anogenital region, as well as those on the sites of trauma need be so treated.

In case of the adult, nevi need not be removed unless they show: (1) signs of rapid growth, change of color, infiltration of pigment into the surrounding tissue, ulceration, bleeding, inflammation, or satellite adenopathy (in other words, signs indicating possible malignant change); (2) features indicating junctional activity (groups 3 and 4) at sites of trauma; (3) clinical evidence of junctional activity persisting in the later decades (40 years); (4) a distribution on sites where maturity is not likely to develop, namely, the hands, feet, and anogenitalia. However, lesions on the palms and soles may be so located (sites of pressure) and so numerous that removal may be impractical.

In childhood most nevi are immature. Because in prepuberty rapid maturity can be anticipated and, also, because the incidence of true melanoma is exceedingly low in childhood, there is no prophylactic indication for the removal of nevi except: (1) clinical evidence of malignant change; (2) signs that the lesion is subject to trauma; and (3) lesions on the palms, soles, and anogenital regions where maturity is not to be anticipated.

The only one way to remove a lesion with clinical signs of junctional activity is by total surgical excision with a reasonably wide border of normal skin and deep enough to reach into the subcutaneous tissue. This must be followed always by biopsy. The last requirement is absolutely essential to prove that the lesion was not already malignant at the time of its removal. Failure to do this has resulted in the misconception that tampering with these nevi gives rise to malignancy. This false notion has developed because of failure to prove the benignity of the lesion by histologic means at the time of the original treatment. No case in the literature has been reported of malignancy having developed in a histologically proved benign nevus following removal.[8] It is our opinion that, when malignancy develops after the treatment of a so-called "benign lesion," malignancy was already present at the time of the original intervention.

Lesions without clinical signs of junctional activity may be treated for cosmetic reasons. In all cases, however, one must have histologic control. All elevated lesions of this type, that is, domes, pedunculated, and polypoid lesions can be snipped or sliced off at the level of the skin and the base lightly electrodesiccated. The removed superficial portion must then be examined histologically. This is practicable because junctional activity is always in the superficial part of the lesion while the buried remaining base of the lesion is the mature intradermal portion. In the event of a mistaken clinical diagnosis, particularly in regard to early or questionable malignancy, the lesion can be appropriately re-excised with a sufficient border of normal skin and subcutaneous tissue.[9]

It is obvious that flat lesions and slightly elevated lesions, even those considered to be without junctional activity, must be excised in toto; otherwise no histologic control can be had.

There seems to be a widespread fear that excision into or biopsy of a melanoma precipitates its spread. One need only point out the great variability in the behavior of these lesions and their totally unpredictable metastatic periods from 0 to 20 years to demonstrate that such an assertion cannot be proved. Because melanoma in its early stages is so often misdiagnosed[7] and especially because benign lesions are so frequently mistaken for melanoma, unless the lesion is small, so that it can be totally excised without mutilation or cosmetically undesirable effects, a partial biopsy should always be preliminary to more extensive surgery.

SUMMARY

The term "melanocytic nevus" is suggested as more satisfactory than the designation pigmented nevus or common "mole" because the lesion is made up of melanocytes. This name will differentiate it from pigmented spots of other cellular constituents with which it is often confused.

Approximately 50 per cent of the melanomas that arise on the skin start in melanocytic nevi that present the pathologic picture of junctional activity. Melanocytic nevi where junctional activity is absent do not ordinarily give rise to malignancy.

Based on clinical features the presence or absence of junctional activity in melanocytic nevi can be clinically predicted with a fair degree of reliability. It becomes possible, therefore, with reasonable accuracy, to recommend for prophylactic removal those lesions which are potentially malignant.

Melanocytic nevi having junctional activity are apt to be flat, slightly elevated, elevated with a surrounding flat pigmented ring, or verrucous in appearance; while those that are elevated, sessile, polypoid, or pedunculated are usually free of junctional activity.

Junctional activity tends to be lost with age in most nevi. It is likely to be retained, however, in nevi on the hands, feet, and the anogenitalia.

It is felt that melanocytic nevi may be prophylactically removed when they (1) show signs of incipient malignancy, (2) are present on the hands, feet, and anogenitalia, (3) are subject to trauma, and (4) show signs of having retained junctional activity after the age of 40.

All nevi removed prophylactically should be adequately excised and examined histologically.

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CHRONIC "BENIGN ASEPTIC MENINGITIS"

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THE type of meningitis in which the spinal fluid is bacteria-free and shows a pleocytosis consisting chiefly of mononuclear cells constitutes a syndrome to which a variety of names have been applied. The term "acute aseptic meningitis" was suggested by Wallren,[1] in 1925, for such cases when the spinal fluid Wassermann complement fixation test was negative, the course benign, and the presence of chronic bacterial or mycotic infection in the brain excluded.

In 1934, during the course of investigations of the St. Louis encephalitis epidemic, Armstrong and Lillie[2] recovered from monkey brain a virus which produced systemic illness in mice and guinea pigs and a meningitic illness in monkeys. Protective antibodies against this virus were subsequently found in the sera of some patients with aseptic meningitis by Rivers and Scott,[3] and a serologically identical virus was recovered from their spinal fluids. This virus has subsequently been referred to as either "Armstrong's virus" or the "virus of lymphocytic choriomeningitis (LCM)."[4]

It has become apparent that Armstrong's virus is not the causative agent in all instances of this type of illness, and, in fact, accounts for only 5 to 10 per cent of cases of aseptic meningitis. It is, therefore, inappropriate to apply the term "acute lymphocytic choriomeningitis" except where this virus is recovered from the spinal fluid or implicated by serologic studies. When the causal agent is not identified in this type of illness the term "acute aseptic meningitis" is preferable since it implies no specific etiology and simply designates a clinical syndrome.

A review of the literature makes it apparent that the prefix "acute" is not properly applied to all cases of aseptic meningitis. Although the meningitis is usually abrupt in onset and runs a brief course with spontaneous recovery and prompt return of the spinal fluid to normal, there have been instances where the illness has followed a more prolonged course[5,8,13,19,20] or has been followed by one

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or more relapses.[22,29] There have also been reports of persistence of spinal fluid abnormalities long after clinical recovery from the illness (Table VI).

Three cases of aseptic meningitis which followed unusually chronic but eventually benign courses have been observed at the Johns Hopkins Hospital. It is the purpose of this paper to describe and discuss these cases together with 3 additional cases seen elsewhere and not previously reported.

CASE REPORTS

CASE 1.—(Baltimore City Hospital History No. 38567.) Relapsing meningitis with probable B.F.P.* phenomenon in spinal fluid, duration at least 9 months. G. A., a 17-year-old Negro, had been in good health until 3 weeks before admission to the hospital in April, 1938. He then developed rhinitis, cough, and a painful swelling in the left inguinal region. Three days before admission he began to complain of weakness and malaise, night sweats, severe headaches, and stiffness of the neck.

On physical examination, he appeared acutely ill. The oral temperature was 104° F., pulse 60 per minute, and blood pressure 130/95. He was conscious and normally oriented. There was redness of the pharynx and generalized lymphadenopathy with tenderness of the inguinal nodes. Kernig's sign was positive, and tendon reflexes throughout were sluggish. There were no other neurologic abnormalities. No genital lesions were found, and the remainder of the examination was unremarkable.

Laboratory data: Urine, no albumin or sugar; occasional R.B.C.'s were seen on two occasions. Blood, R.B.C. 4.23 million per cubic millimeter, W.B.C. 7,750, 43 per cent polymorphonuclears, 2 per cent myelocytes, 51 per cent normal lymphocytes, 3 per cent monocytes. The blood S.T.S.† was negative. A chest radiograph was normal, and a Frei test was negative. The spinal fluid findings are shown in Table I.

Course: The headache and neck stiffness had decreased in severity by the second hospital day, and the patient was completely asymptomatic after 7 days. The temperature remained slightly elevated for 13 days. A diagnosis of syphilitic meningitis was made although it was noted that the spinal fluid complement fixation test was less strongly positive on the seventh hospital day than it had been on admission. Neoarsphenamine therapy was started in April, 1938, and during the next 4 months he received a total of 8.4 Gm. of this drug. Six days after arsenical therapy was begun, the spinal fluid complement fixation test became negative and remained so. The S.T.S. was repeatedly negative except in May, and June, 1938, when the Eagle test gave weakly reactive results.

He remained well throughout this period of observation except for two brief relapses which occurred 4 and 6 months after the initial illness. In these he developed pyrexia, grossly abnormal mental behavior, and headache and neck stiffness which led to his readmission to the hospital on each occasion. On both readmissions to the hospital the fever and other symptoms disappeared within 2 days although the spinal fluid cell count and protein concentration remained elevated. An air encephalogram performed during his third admission to the hospital yielded normal findings.

The patient was last examined 10 weeks after the third hospitalization, i.e., 9 months after his original illness. At that time he was entirely well; the spinal fluid cell count had returned to normal, but the protein remained markedly elevated. The patient was lost from further observation.

Comment.—In retrospect, it seems unlikely that this patient had syphilitic meningitis. The spinal fluid complement fixation test had weakened before therapy was begun, and it became negative only 6 days later. The blood S.T.S. was weakly reactive on two occasions and negative on eight. Unfortunately,

*B.F.P. = Biologic false positive in serologic tests for syphilis.
†S.T.S. = Serologic test for syphilis.

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TABLE I. SPINAL FLUID FINDINGS IN CASE 1

DATE	PRESSURE (MM. H_2O)	LEUKOCYTES/MM.^{3}		PROTEIN (MG. %)	PANDY	MASTIC	COMP. FIX., SYPHILIS (C.C.)			SUGAR (MG. %)
		TOTAL	MONONUCLEAR				0.2	0.4	1	
4-23-38	240	1,000	650		+		+	+	+	
4-27-38	315	1,111	1,090		+	1455555421		+	+	34
5-18-38	300	318	300		+	5555555210	0	0	0	
8-14-38	250	290	275		++++	5555555522	0	0	0	
11- 7-38	250	82	79	188	++++	—	0	0	0	
1-19-39	—	3	3		++++	—				

serologic methods (the treponemal immobilization test and its derivatives) for the identification of biologic false positive reactions for syphilis were not available at that time. Nevertheless, it is believed that this was a case of aseptic meningitis with biologic false positive reactions for syphilis in blood serum and spinal fluid, accompanied by other abnormalities which persisted for at least 9 months.

CASE 2.—(J. H. H. No. 158832.) Relapsing meningitis with B.F.P. phenomenon in the spinal fluid, duration at least 17 months, complicated by pregnancy. M. W., a 22-year-old Negro woman, was first seen in the prenatal clinic in December, 1938, when she was 5 months pregnant. She felt well, but a temperature of 99.4° F. and slight generalized lymphadenopathy were noted. Her past history was uneventful save for typhoid fever at the age of 11 and convulsions just before delivery in a previous pregnancy at the age of 19. The blood S.T.S. was negative.

One week after the initial examination she experienced a sudden chill and went to bed where she remained until admitted to the hospital 3 weeks later. During that time she developed, in succession, anorexia, vomiting, severe headache, and vague abdominal pains.

On physical examination at the time of admission on Jan. 10, 1939, she appeared acutely ill. Her temperature was 104° F. orally, pulse 120, respirations 20, and blood pressure 110/60. She was conscious and normally oriented. There was minimal neck stiffness. Hypoactive tendon reflexes and slight blurring of the left optic disk were also noted. The remainder of the examination was negative except for the signs of pregnancy.

Laboratory data: Urine, normal. Blood, the hemoglobin was 11 Gm. per 100 ml. of blood; the white cell count was 10,000 per cubic millimeter with 70 per cent polymorphonuclears, 19 per cent lymphocytes, and 11 per cent monocytes. The blood S.T.S. was again negative. A chest radiograph was normal. Tuberculin skin test was negative. Skull and sinus radiographs were normal. Heterophile antibodies were absent. Brucella agglutination tests and serologic tests for lymphocytic choriomeningitis were negative. The spinal fluid findings are shown in Table II.

Course: During the first 3 days in the hospital her oral temperature varied irregularly between 99° and 103° F. Examination on the third day revealed marked neck stiffness, positive Kernig's sign, and jerky external ocular movements. Sulfanilamide therapy was started that day and was continued for 17 days. On the fourth day she became afebrile, she began to feel better, and the physical signs rapidly regressed. The spinal fluid complement fixation test for syphilis which was positive on admission became progressively weaker and was negative for the first time on the twentieth hospital day. On that day, Jan. 31, 1939, she went home feeling well, although the spinal fluid still contained 60 lymphocytes per cubic millimeter.

Two days later she awoke with severe right parietal headache, became feverish again, and developed neck stiffness. She was readmitted to the hospital on Feb. 4, 1939, with temperature

TABLE II. SPINAL FLUID FINDINGS IN CASE 2

DATE	PRESSURE (MM. H_2O)	LEUKOCYTES/MM.^{3}		PROTEIN (MG. %)	PANDY	MASTIC	COMP. FIX., SYPHILIS (C.C.)			SUGAR (MG. %)
		TOTAL	MONONUCLEAR				0.2	0.4	1	
1-10-39	170	300	300	100	+++	4443210000	+	+	+	35
1-12-39		1,165	880	75	++		0	+	+	
1-18-39	70	486	396				0	0	+	
1-30-39		60	60	25	++	5554321000	0	0	+	
2- 4-39		609	519	100	+++	4554321000	0	0	0	
2-19-39	150	590	531	175	++++	4555432100	0	0	0	
3- 2-39	100	614	600	200	++++	4454321000	0	0	0	
5-23-39		316	316	120	++++	3444432100	0	0	0	
1- 5-40		17	17	75	++	4432100000				
6-19-40		5	5	75	+++	5532100000	0	0	0	

Repeated cultures of the spinal fluid were negative, and guinea pig inoculation for T.B.C. was negative on 4 occasions.

103.4° F., pulse 120 per minute, respirations 22 per minute, and blood pressure 106/54. She again had neck stiffness and now also had photophobia. The following day she became afebrile, and her clinical status rapidly returned to normal.

She remained in the hospital until 2½ months later, and on April 18, 1939, was spontaneously delivered of a normal child whose S.T.S. was negative. The patient's spinal fluid remained abnormal, and when examined on Jan. 5, 1940, a year after the initial illness, it still contained 17 lymphocytes per cubic millimeter and 75 mg. per cent of protein. Six months later, the cell count was normal but the protein concentration remained elevated, and the first zone of the colloidal mastic curve remained positive. The patient was last examined 2 years after the original attack of meningitis, and she appeared to be in good health. She was subsequently lost to follow-up.

Comment.—This patient had a transient positive spinal fluid Wassermann complement fixation test which reverted to negative within 20 days without specific therapy. Her clinical illness lasted about one month and was complicated by a single brief relapse and by pregnancy which went to full term with delivery of a normal child. Spinal fluid abnormalities persisted for at least 17 months, but the patient was lost from observation after 2 years and the spinal fluid was not again examined.

CASE 3.—(J. H. H. No. 153394.) Meningitis in a child followed by spinal fluid abnormalities for 3½ years. A. M. H., a 4-year-old Negro child, was admitted to the Sydenham Hospital, Baltimore, in October, 1938, because of severe prostration, fever, neck stiffness, and anorexia for 4 days. There was a history of cough and associated vomiting for 2 weeks prior to hospitalization, and 4 other children in the home were thought to have pertussis. There was no history of convulsions.

Physical examination: On admission the patient appeared adequately nourished, irritable, and acutely ill. Rectal temperature was 103.2° F., pulse 140 per minute, and respirations 60 per minute. She coughed occasionally, but there was no whoop and no vomiting. Kernig's sign was postive and opisthotonus was present. Rales were heard at the right lung base.

Laboratory data: A chest radiograph showed patchy infiltration near both hilar regions, interpreted as bronchopneumonia. Blood: the hemoglobin was 13 Gm. per 100 ml. of blood

the white cell count was 6,800 per cubic millimeter, with 26 per cent polymorphonuclears, 68 per cent lymphocytes, and 6 per cent monocytes. The blood S. T. S. was negative. Agglutination tests for salmonella, typhoid and paratyphoid, proteus, and brucella organisms were all negative. Sputum culture and cough plate for *Hemophilus pertussis* were negative. The urine was normal. The spinal fluid changes are shown in Table III.

TABLE III. SPINAL FLUID FINDINGS IN CASE 3

DATE	PRESSURE (MM. H_2O)	LEUKOCYTES/MM.^{3}		PROTEIN (MG. %)	PANDY	MASTIC	COMP. FIX., SYPHILIS (C.C.)			SUGAR (MG. %)
		TOTAL	MONONUCLEAR				0.2	0.4	1	
12- 5-39		470	210	61	++		0	0	0	28
1-16-40		552	552		+++		0	0	0	
2-13-40	150	508	310	200	++++	5555432100	0	0	0	
4-19-40		800	590		+					
2-26-41		3	3	25	+	4321000000	0	0	0	
5- 8-42		6	6	30	+	3210000000	0	0	0	
6-25-43		0	0	25	+	3210000000	0	0	0	
7-14-44		0	0	17	0	2100000000	0	0	0	
1-30-51	100	0	0	12	0	0000000000	0	0	0	

Course: She was given sulfonamide therapy for 9 days. On the fourth day her temperature returned to normal, and she seemed well. During the subsequent 2 months she remained well but on 3 occasions was febile for periods of 24 to 48 hours.

The spinal fluid, however, continued to contain between 300 and 750 white cells of which an increasingly large proportion were mononuclear cells. The blood and spinal fluid tests for syphilis were repeatedly negative. She was transferred to the Harriet Lane Clinic of the Johns Hopkins Hospital where the agglutination studies reported above were done. She was eventually discharged 6 months after the onset of the illness at which time the spinal fluid still contained 210 mononuclear cells per cubic millimeter and 154 mg. per cent of protein.

Six months later the cell count and protein content had returned to normal levels, but the Pandy and mastic curve continued to show an abnormal protein pattern for over 3 years. Subsequent spinal punctures 7 and 10 years later revealed entirely normal fluids. The patient has remained well up to the present time (April, 1956) except for a hemolytic transfusion reaction during her second pregnancy in 1954.

Comment.—At first, it was suspected that this child might have encephalitis secondary to pertussis, but the predominance of the meningitic features made this diagnosis unlikely. The clinical illness was relatively brief with minor febrile relapses over a period of 2 months, but abnormalities were still present in the Pandy test and mastic curve more than 3 years later.

CASE 4.—(J. H. H. No. 152018.) Meningitis with protracted clinical course (2 months) and transient motor paralyses, with spinal fluid abnormalities persisting for 5 months. J. V., a 22-year-old Negro woman was admitted to the hospital on March 4, 1955, with a history of continuous severe headache for 8 days. She later stated that the lesions which were found on examination of the external genitalia had been present for several weeks. There was a past history of pelvic inflammatory disease, and gonococcal vaginitis was reported to have been diagnosed at 5 and again at 9 years of age, but confirmation of this report was not obtained.

On physical examination at the time of admission the oral temperature was 103° F., pulse 80, blood pressure 110/70. She appeared dehydrated but otherwise in a good nutritional state. She was difficult to rouse and keep awake. The conjunctivae showed bilateral injection, but the ocular media and fundi were normal. There was no generalized lymphadenopathy. Moderate nuchal rigidity and a positive Kernig's sign were present. There were several nonvesicular erosions about 1 cm. in diameter on the skin of the labia majora.

Laboratory data: The urine was normal except for the presence of many white blood cells in a catheterized specimen on admission. Blood: hematocrit 36 per cent, W.B.C. 14,000, polymorphonuclears 52 per cent, lymphocytes 38 per cent, monocytes 9 per cent. The W.B.C. count subsequently varied within the range 8 to 16,000 with a normal differential. The blood S.T.S. was negative. Cephalin flocculation was 2 plus, thymol turbidity was 4.3 units, the alkaline phosphatase was 9.6 Bodansky units, and the serum bilirubin was 0.8 mg. per cent. An L. E. cell preparation was negative. The ECG and chest radiograph were normal. Dark-field examination and culture of the genital lesions demonstrated no specific organisms; and biopsy of one of them showed nonspecific inflammatory changes and no herpetic inclusions. Serologic tests for lymphocytic choriomeningitis, lymphopathia venereum, leptospirosis, herpes, and mumps were negative on several occasions. Frei and Ito skin tests were weakly positive; the histoplasmin skin test was negative. Ventriculograms and a left cerebral arteriogram were interpreted as normal. The spinal fluid findings are shown in Table IV.

Course: Throughout her hospital stay of 2 months the patient ran an intermittent fever up to 103° F. During the periods of high fever she complained of severe headache and was difficult to rouse. On one occasion she complained of diplopia for a few hours, but the physical findings were equivocal. On another occasion she had signs of a mild right hemiparesis which had resolved by the following day.

TABLE IV. SPINAL FLUID FINDINGS OF CASE 4

DATE	PRESSURE (MM. H_2O)	LEUKOCYTES/MM.^{3}		PROTEIN (MG. %)	PANDY	MASTIC	COMP. FIX., SYPHILIS (C.C.)		SUGAR (MG. %)
		TOTAL	MONONUCLEAR				0.2	1.0	
3- 4-55		380	260	61	++	2211000000	0	0	45
4- 2-55	80	82	80	40	+	1110000000	0	0	61
5- 5-55		230	—	57		2210000000	0	0	
5-19-55	125	97	60	57	++	2210000000	0	0	
6- 1-55		123	81	—	+	1221000000	0	0	
8-11-55		50	50	36	+		0	0	

Repeated cultures of the spinal fluid were negative, and guinea pig inoculation for tubercle bacilli was negative on two occasions.

Aureomycin was given during the illness but did not appear to influence its course. She left the hospital at her own request after 2 months, although she was still intermittently febrile and still showed spinal fluid abnormalities. She was seen one month after discharge from the hospital and then complained of malaise and headache, but 2 months later, i.e., 5 months after the onset of the illness, she felt well and clinical examination was normal. Examination of the spinal fluid at this time, however, revealed 50 mononuclear cells per cubic millimeter and normal protein content. The patient was subsequently lost to follow-up.

Comment.—This patient had a meningitic illness of more than 2 months' duration, with spinal fluid abnormalities persisting at least 5 months. The serum alkaline phosphatase level was elevated and a 2 plus cephalin flocculation reaction obtained, but these tests were not repeated.

CASE 5*.—Four attacks of meningitis during a period of 8 years. This patient, a 34-year-old white man, was admitted to a hospital in Washington, D. C. in July, 1953, for study. At that time he was symptom-free, and physical examination was negative. He gave a history of 5 acute illnesses between 1945 and 1953.

*Data on this case supplied by R. C. Parker, Captain (MC) USN, Chief of Medicine, U. S. Naval Hospital, Bethesda, Md.

First Attack (August, 1944): The patient was admitted to a hospital in the Washington area with a history of 3 days of headache, dizziness, restlessness, insomnia, and aching in the loins. On examination, he was febrile and had a pink macular rash on the hands, wrists, and feet. The pharynx was injected, the left optic disk was slightly blurred, and Kernig's sign was positive. Tendon reflexes were sluggish. The spinal fluid was under increased pressure but contained no cells at this examination. A diagnosis of Rocky Mountain spotted fever was entertained, but agglutination tests were negative. He became afebrile on the eighth hospital day, and the rash had cleared with exfoliation by the end of the second week.

Second attack (August, 1947): The patient was readmitted with complaints of insomnia, stiff neck, generalized headaches, and photophobia for 24 hours. Temperature was 103° F., the patient was drowsy, the neck was stiff, and there was no rash. Reflexes were hyperactive. Blood count showed 15,150 W.B.C., 74 per cent polymorphonuclears. Spinal fluid pressure was 230 mm.; there were 740 cells per cubic millimeter, 100 per cent mononuclears; sugar 40 mg. per cent; protein 75 mg. per cent. He was treated with a sulfonamide but this was discontinued after 24 hours because of hematuria. On the second day in the hospital he felt better and nuchal rigidity had disappeared by the sixth day.

Third Attack (February, 1950): He was admitted to a hospital in Georgia with complaints of dull bitemporal headache, malaise, chills, and myalgia. Temperature was 101° F. There was neck stiffness and tenderness of the abdominal muscles. His W.B.C. count was 18,150 with 91 per cent polymorphonuclears. Spinal fluid contained 490 cells per cubic millimeter, 97 per cent mononuclears; protein was 193 mg. per cent and sugar 58 mg. per cent. Serologic studies for mumps, lymphogranuloma venereum, and leptospirosis were negative. Chest radiograph was normal. He was given Aureomycin for 5 days. The temperature fell to normal levels 12 hours after the institution of this therapy, and all symptoms regressed rapidly.

Fourth attack (March, 1951): At this time the patient was in Japan and was admitted to a hospital with a recurrence of frontal headaches, malaise, chills, fever, and neck stiffness. W.B.C. count was 17,500 with 74 per cent polymorphonuclears. Spinal fluid pressure was 270 mm. There was a pleocytosis of 445 cells, 54 per cent polymorphonuclears, 46 per cent mononuclears; sugar 47 mg. per cent, and protein 71 mg. per cent. Penicillin and sulfadiazine were given and improvement occurred by the third day.

Fifth attack (January, 1953): He was again admitted to a hospital in Japan with headache, malaise, anorexia, and neck pain. The temperature was 103° F. There was neck stiffness and blurring of the disk margins. Spinal fluid showed 60 cells per cubic millimeter, 96 per cent mononuclears, and a protein content of 152 mg. per cent. The headache persisted for 15 days, and on the fourth day a positive left Babinski sign was found to be present which persisted till the fifty-third hospital day.

In July, 1953, at a time when the patient was asymptomatic, a careful physical examination was negative except for reddening and slight blurring of the optic disks. Laboratory investigations revealed no definitely abnormal results. There was some increased density of the left maxillary sinus on x-ray, the vital capacity was slightly reduced, and the EEG was of low voltage. The colloidal gold curve of the C.S.F. showed mid-zone elevation, but the fluid was otherwise entirely normal. Examination of the urine including test for porphyrins was normal, and blood counts were within normal limits. Liver function tests, blood tests for syphilis, and the *Treponema pallidum* immobilization (T.P.I.) test were all negative. No parasites could be found on 3 stool examinations. Radiographs of the chest, skull, vertebral column, and long bones revealed no abnormality. The ECG and B.M.R. were normal. Complement fixation tests for lymphocytic choriomeningitis, toxoplasmosis, histoplasmosis, blastomycosis, and coccidiodomycosis, and agglutinations for leptospirosis were all negative. The Frei test and skin tests for histoplasmosis and coccidioidomycosis were negative.

Comment.—This patient had 4 attacks of aseptic meningitis during a period of 9 years. Each attack was relatively brief and without sequelae except for the fifth attack in which he developed a positive Babinski sign which persisted for nearly two months. The etiology of this patient's disease remains undetermined.

CASE 6.—(New Haven Hospital No. 377184.) Meningitis simulating tuberculous meningitis. R.B.M., a 49-year-old white housewife, was admitted to the hospital in September, 1952, with the complaint of low back pain of sudden onset 6 days earlier, followed by nausea, fever, progressively severe headaches, stiff neck, and difficulty in speaking and swallowing. She had been in good health until the onset of this illness, and no history of contact with tuberculosis was obtained. A goiter at the age of 14 was treated with "brown medicine," and in adult life she had suffered from periodic migraine, the last attack occurring one month prior to the onset of this illness.

Physical examination revealed a temperature of 101° F. and blood pressure of 150/85. Her speech was barely intelligible. There was sialorrhoea and severe nuchal rigidity. Paralysis of palatal movement was almost complete, but the remainder of the neurologic examination was normal.

Laboratory data: The hemoglobin was 14 Gm. per cent, the W.B.C. 11,700 with a normal differential. The urine was normal. The chest radiograph was normal. Nose and throat culture revealed no pathogens. Blood electrolytes, proteins, and N.P.N. were within normal limits. A skin test with P.P.D., second strength, was negative. Complement fixation tests for mumps, lymphocytic choriomeningitis, lymphogranuloma venereum, and herpes were negative during the third week of hospitalization. The spinal fluid findings are shown in Table V.

Course: A presumptive diagnosis of tuberculous meningitis was made following admission, and the patient was given streptomycin 2 Gm. daily and PAS 10 Gm. daily. This was continued for 4 days by which time there was considerable objective and subjective improvement. Because of the prompt improvement and because of the failure to find tubercle bacilli in the spinal fluid, it was felt that the meningitis was more likely to be viral in etiology, and the antituberculous therapy was therefore discontinued on Sept. 18, 1952. Two days later the patient complained of increasing headache and became drowsy again. There was increased nuchal rigidity, and the rectal temperature rose to 103° F. Lumbar puncture at this time revealed 1,670 cells per cubic millimeter of which 77 per cent were polymorphonuclears. Because of her deteriorating condition, chemotherapy was reinstituted on Sept. 20, 1952, and intrathecal streptomycin, 50 mg. daily, was also given. Following this, the patient soon became afebrile, and lumbar puncture revealed a steady fall in the cell count and spinal fluid protein.

One month after the onset of the illness she was well except for continued weakness of the palatal movements and associated nasal speech. On Oct. 15, 1952, she was transferred to Laurel Heights Sanatorium for further assessment and treatment.

TABLE V. SPINAL FLUID FINDINGS IN CASE 6

DATE	PRESSURE (MM. H_2O)	LEUCOCYTES/MM.^{3}		PROTEIN (MG. %)	SUGAR (MG. %)	CORRESPONDING BLOOD SUGAR
		TOTAL	MONONUCLEAR			
9–12–52	"low"	525	390	115	33	71
9–20–52	180	1670	400	100	35	103
9–23–52	216	74	74	66		
9–26–52		72	64	55	43	131
10– 4–52	185	31	31	32	51	
10–14–52	175	35	32	39		
12–20–52		7	7	66		

Spinal fluid culture was repeatedly negative, and guinea pig inoculation for T.B.C. was negative on three occasions.

Clinical examination revealed no new findings on admission, and she was treated with streptomycin, PAS, and isoniazid. Intrathecal streptomycin was discontinued. There was a gradual

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return toward normal of the spinal fluid constituents, and at the last examination 3 months after the start of the illness the fluid contained 7 cells per cubic millimeter and normal protein and sugar values.

The patient recovered strength rather slowly with gradual recovery of palatal movements and voice quality. Neurologic examination 10 weeks after the onset of the illness revealed definite weakness of all major muscle groups of the lower legs. Chemotherapy was discontinued on Dec. 11, 1952, as considerable doubt as to the tuberculous etiology had arisen on clinical grounds and because the results of guinea pig inoculation had been uniformly negative. Slow recovery of muscle strength continued during the next 3 weeks. When last heard from in December, 1956, she was normally active and asymptomatic.

Comment.—This case illustrates the difficulty which may arise in distinguishing viral from tuberculous meningitis when tubercle bacilli are not found on smear or culture of the spinal fluid. Spinal fluid sugar determination in this case suggested a bacterial infection, but the repeated culture and animal inoculation with spinal fluid failed to confirm this, and it must be concluded that this was some other form of meningoencephalitis. While the acute phase of the illness in this patient was not unduly prolonged and the spinal fluid abnormalities were marked for a period of only about one month, nevertheless, full recovery from the effects of the illness was not achieved until more than 3 months after its onset.

DISCUSSION

It is evident that in addition to the well-recognized acute benign forms of aseptic miningitis, there are instances where the illness is prolonged. Study of the literature and of the case histories presented here does not suggest that the chronic form is a distinct entity. Rather the available data point to the probability that aseptic meningitides of several etiologies which usually run an acute benign course may show varying degrees and forms of chronicity including a characteristically acute and brief type of relapse but with ultimate complete recovery.

Lepine[14] called attention to the similarity in the clinical picture of meningitis occurring in the course of the exanthemata, leptospirosis, mumps, herpes simplex, nonparalytic poliomyelitis, and lymphocytic choriomeningitis. This diversity of etiology has been repeatedly confirmed and extended. In recent years, the Coxsackie virus[15] and infectious mononucleosis[16,17] have been incriminated in similar illnesses. Meningitic manifestations have been reported in the course of systemic lupus erythematosus[23] and in sarcoidosis.[24]

Adair, Gauld, and Smadel[18] analyzed the results of examination of sera from 855 cases diagnosed as aseptic meningitis in the U.S. Army. Of the entire series, lymphocytic choriomeningitis accounted for only 9 per cent and mumps for 12 per cent of the cases. Of 114 sera tested for herpes, 5.3 per cent were positive, and of 158 tested for leptospirosis, 7.6 per cent were positive.

The number of cases of aseptic meningitis reported with "chronic" manifestations is too few to allow a statistical analysis of the etiologic agents even if they were known. We were able to find 5 cases in the literature where details were given of prolonged spinal fluid abnormalities. In all 5 of these, the virus of lymphocytic choriomeningitis was isolated or incriminated as the result of

serologic tests (Table VI). Appropriate studies were performed on 4 of the 6 patients in our series, but in none could this virus (LCM) be incriminated. In no case in the present series was any etiologic agent discovered. Mollaret[25] has described a benign recurrent form of meningitis which differs from the cases presented here chiefly by reason of a rapid return to normal of the spinal fluid after each meningitic episode. An unidentified filterable agent was recovered from the spinal fluid of one of his cases by the inoculation of embryonated chicken eggs. It is not yet clear whether Mollaret's cases constitute a distinct entity or whether this virus is widely distributed.

TABLE VI. CASES REPORTED WITH PROLONGED SPINAL FLUID ABNORMALITIES

NAME OF AUTHOR	SEX	AGE	RELATIONSHIP TO LYMPHOCHORIO-MENINGITIS	RESIDUAL MANIFESTATIONS	LATE SPINAL FLUID FINDINGS
Chang[19] Hisoh-Teh	M	22	Virus isolated	Severe headaches necessitating 58 lumbar punctures during hospitalization over 15 months	15 months after onset 40 white cells/mm.^{3} C.S.F.
Howard[20]	M	26	Virus isolated	Complained of severe headaches and stiff back for several months after discharge from hospital	4½ months after onset 53 white cells/mm.^{3} C.S.F. 12 months after onset 10 white cell/mm.^{3} C.S.F. 51 mg. % protein
Viets[12]	M	18	Antibodies detected	No residual symptoms	4½ months after onset 87 mg. % protein 2 white cells/mm.^{3} C.S.F.
Skogland[21]	M	49	Antibodies detected	Persistent headaches and low-grade fever over 12 months requiring 3 admissions to hospital	16 months after onset 44 white cell/mm.^{3} C.S.F. 200 mg. % protein
Leichenger[22]	M	18	Antibodies detected	4 recurrences of meningitic symptoms over a period of 3 months	3 months after onset during last recurrence 840 white cells/mm.^{3} C.S.F. 300 mg. % protein

Two of the 6 cases presented here had transient positive complement fixation tests for syphilis in the spinal fluid. It has already been indicated that there was good reason for believing that neither of these patients had syphilis. Green, Sweet, and Prichard[26] reported 2 cases of lymphocytic choriomeningitis who had transient positive Wassermann reactions in the spinal fluid and who were thought not to have syphilis. Scott, Reynolds, and Mohr[27] drew attention to the frequency with which a biologic false positive test for syphilis could occur in a variety of types of meningitis (Case 2 in the present report was used as in illustration by these authors). More recently, Zellman and Lutz[28] confirmed the occurrence of this phenomenon in 3 cases of nonsyphilitic meningitis by means of the *Treponema pallidum* immobilization test.

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There is no evidence that chemotherapy or any other form of treatment was beneficial in the present cases. In some patients, severe headaches seemed to be relieved by repeated lumbar puncture, but in others the same procedure was ineffective. When a patient has become asymptomatic but has persistent spinal fluid abnormalities, the problem of continued rest versus a return to activity arises. Study of the cases in the present series, while by no means conclusive, suggests that the persistence of spinal fluid abnormalities indicates a liability to relapse, but there is nothing to indicate that the likelihood of relapse would be diminished by bed rest.

SUMMARY

Six cases of lymphocytic meningitis with chronic or intermittent manifestations are presented. The etiologic agents were not identified. Similar cases described in the literature are discussed and summarized in tabular form. Two of the cases here presented had transient positive spinal fluid tests for syphilis; these are believed to have been biologic false positive reactions. Prolonged abnormality of the spinal fluid cell count and protein may continue long after clinical recovery from aseptic meningitis. It is suggested that such abnormalities should be regarded as a warning of liability of meningitic relapse. There is no evidence that continued elevation of the spinal fluid cell count and protein, whether or not associated with meningitic relapses, carries with it a less favorable long-term prognosis than that of the acute forms of aseptic meningitis.

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INFLUENCE OF A MODERATELY COLD ENVIRONMENT ON VENOUS PRESSURE IN THE SUPERFICIAL VEINS OF NORMAL YOUNG MEN AND PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

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IN PREVIOUS studies, a hot and humid environment was found to increase the venous pressure in the superficial veins of normal young adult men[1,2] and patients with chronic congestive heart failure[2] and to precipitate congestive failure in patients with cardiac disease.[2-5] Furthermore, a cool environment was fortuitously found to precipitate acute left ventricular congestive heart failure in a patient with syphilitic aortic disease.[6] The influence of a cold and cool environment on the venous pressure in the superficial veins of normal man has been studied previously.[7-11] The present study was undertaken not only to re-evaluate this phenomenon in normal man but also to investigate the responses of the venous system to this stimulus in patients with chronic congestive heart failure and elevated systemic venous pressure. These studies seemed particularly appropriate since the veins have been shown to play an active role in the circulation.[12] In a patient with an already elevated venous pressure in the systemic and pulmonary circulations, sudden cooling of the body may possibly cause venoconstriction and increase venous pressure further, with resultant exacerbation in the degree of congestive failure.

MATERIALS AND METHODS

Twenty-eight normal white male medical students (21 to 32 years of age) and 15 Negro patients with chronic congestive heart failure (Table I) rested in the supine position in a hospital type bed in a comfortable atmosphere (temperature about 25° C.; relative humidity about 60 per cent) with the median basilic vein at heart level. The subjects with failure were under treatment, which included digitalization. All subjects were clothed only in cotton shorts, with a cotton sheet covering the pelvis and upper third of the thighs; the breasts of female patients were also covered. Arterial blood pressure was recorded with

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a mercurial sphygmomanometer, and pulse and respiratory rates were obtained. Venous pressure was measured with the phlebomanometer.[13] The subjects were then transferred to an adjacent room, with environmental temperature of about 12° C. and relative humidity of about 73 per cent (range 56 to 90 per cent), where they rested in bed, with the same type of clothing and covering, until they were about to experience a rigor. This usually developed in about 30 minutes (range 10 to 85 minutes) in the normal subjects. The physiologic measurements were again made. In 3 normal subjects, these recordings were obtained during a mild rigor. The patients with congestive failure were not chilled sufficiently to produce a rigor for fear that acute pulmonary edema or left ventricular failure might be precipitated.

RESULTS

Results are summarized in Tables I, II, and III and in Figs. 1 and 2.

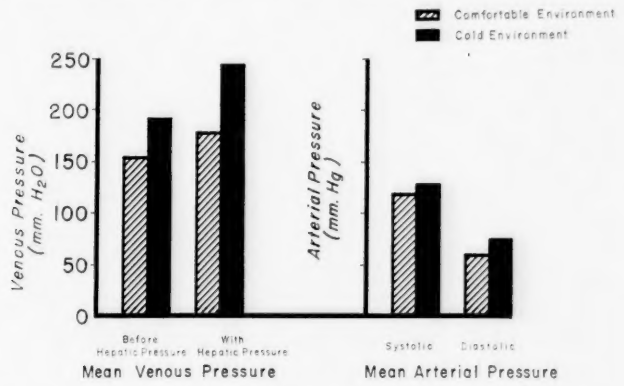

Fig. 1.—Influence of a moderately cold environment on venous pressure in normal man. The mean venous pressure is shown before and during hepatic pressure in a comfortable, as well as cold, environment for 28 normal young adults.

Venous Pressure: Normal Subjects.—The venous pressure rose in response to the colder environment in all normal subjects except one (Subject 9, Table II), in whom it declined in two different experiments. The mean change for 28 normal subjects was +39 mm. H_2O (26 per cent), with extremes of −70 and +137 mm. Hg (−35 and +86 per cent) (Table II, Fig. 1). The increase in venous pressure tended to be even greater during rigor. Whereas all the superficial veins were previously prominent, they became narrowed or constricted in the cold atmosphere, indicating venoconstriction.

The response of the hepatojugular reflux test was more pronounced in the cold environment than in the comfortable one (Table II, Fig. 1). The mean increase in venous pressure with pressure over the hepatic area for the subjects in the comfortable environment was 22 mm. H_2O (14 per cent), with a range of 0 to 80 mm. H_2O (0 to 58 per cent), and for the same subjects in the cool environment, the mean rise was 50 mm. H_2O (27 per cent), with a range of 13 to 110 mm. H_2O (5 to 53 per cent) (Table II, Fig. 1).

Patients With Chronic Congestive Heart Failure.—The response of the venous pressure of the 15 patients with chronic congestive heart failure to the cold

environment was not as consistent as for the younger normal subjects, but in certain individual instances there was a pronounced increase in venous pressure (Table III, Fig. 2). Although the mean percentile rise in venous pressure was

TABLE I. CLINICAL DATA FROM 15 NEGRO PATIENTS WITH CONGESTIVE HEART FAILURE

SUBJECT NO.	SEX	AGE (YEARS)	DIAGNOSES	RESPONSE TO COOL ENVIRONMENT
1	F	43	RHD,* CHF†; probable bronchiectasis	Tolerated cold well
2	F	18	RHD with mitral insufficiency; auricular fibrillation; CHF	Tolerated cold moderately well
3	F	65	HCVD‡; auricular fibrillation; CHF	Tolerated cold well
4	M	48	HCVD; auricular fibrillation; CHF	Tolerated cold well
5	M	62	HCVD; CHF	Tolerated cold moderately well
6	F	68	HCVD; ASHD§; anemia; CHF	Tolerated cold poorly; became much more dyspneic and somewhat mentally confused in cold room
7	F	62	HCVD; ASHD; diabetes; CHF	Tolerated cold moderately well
8	M	55	ASHD; old myocardial infarction; auricular fibrillation; CHF	Tolerated cold well except for increased coughing
9	F	26	RHD with mitral stenosis and insufficiency; auricular fibrillation; CHF	Tolerated cold moderately well
10	F	61	ASHD; diabetes; CHF	Tolerated cold poorly; became much more dyspneic in cold room
11	M	57	ASHD; coronary insufficiency; CHF	Tolerated cold well
12	F	43	RHD; auricular fibrillation; CHF	Tolerated cold poorly. After only 5 minutes in cold room, CHF noted; acute pulmonary congestion necessitating termination of study. Patient gradually improved over the ensuing 30 minutes in comfortable environment.
13	F	47	RHD (?); possible sarcoid and cor pulmonale; CHF	Tolerated cold moderately well
14	F	59	HCVD; CHF	Tolerated cold somewhat poorly; became definitely more dyspneic
15	M	73	ASHD with arteriosclerosis; RHD; HCVD; CHF	Tolerated cold moderately well

*Rheumatic heart disease.
†Congestive heart failure.
‡Hypertensive cardiovascular disease.
§Arteriosclerotic heart disease.

less striking in the patients with venous hypertension than in the normal subjects, the absolute mean increase in mm. H_2O was essentially the same (Tables II and III). There was a mean change of +41 mm. H_2O (16 per cent), with extremes of −21 and +106 mm. H_2O (−7 and +43 per cent), for the 15 patients with congestive failure. No increase in pressure was observed in 3 patients, perhaps because of insufficient cooling for fear of precipitating acute pulmonary edema. Venous pressure in the median basilic vein of one patient increased over 100 mm. H_2O. The mean increase in venous pressure as a result of the hepatojugular reflux test in the patients with congestive failure in the comfortable environment was 118 mm. H_2O (48 per cent), with a range of 80 to 230 mm. H_2O (26 to 75 per cent). For the same patients in the cold environment a mean rise of 121 mm. H_2O (41 per cent) was observed, with a range of 60 to 215 mm. H_2O (25 to 75 per cent).

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TABLE II. INFLUENCE OF MODERATELY COLD ENVIRONMENT ON VENOUS PRESSURE IN NORMAL YOUNG ADULT SUBJECTS

SUBJECT NO.	VENOUS PRESSURE			CHANGE IN VENOUS PRESSURE WITH HEPATIC PRESSURE	
	COMFORTABLE (MM. H_2O)	COLD (MM. H_2O)	CHANGE (MM. H_2O)	COMFORTABLE (MM. H_2O)	COLD (MM. H_2O)
1	155	183	28		
2	135	199	64		
3	135	243	108		
4	155	235	80		45
5	149	168	19		85
6	137	176	39	0	40
7	161	205	44	27	43
8	170	205	35		45
9	200	130	−70	32	38
10	160	297	137	0	45
11	145	160	15	15	80
12	165	182	17	38	25
13	201	241	40	13	13
14	170	210	40	30	85
15	124	150	26	10	100
16	150	195	45	0	45
17	132	150	18	30	
18	141	175	34	35	55
19	164	209	45	10	45
20	111	179	68	27	30
21	159	220	61	42	30
22	169	182	13	15	15
23	184	190	6	15	14
24	169	202	33	52	50
25	165	171	6	10	35
26	139	180	41	80	95
27	160	163	3	15	20
28	137	214	77	0	110
Mean	154	193	39	22	50
Extremes	111	130	−70	0	13
	201	297	137	80	110

TABLE III. INFLUENCE OF MODERATELY COLD ENVIRONMENT ON VENOUS PRESSURE IN SUBJECTS WITH CHRONIC CONGESTIVE HEART FAILURE

SUBJECT NO.	VENOUS PRESSURE			CHANGE IN VENOUS PRESSURE WITH HEPATIC PRESSURE	
	COMFORTABLE (MM. H_2O)	COLD (MM. H_2O)	CHANGE (MM. H_2O)	COMFORTABLE (MM. H_2O)	COLD (MM. H_2O)
1	221	236	15		60*
2	172	238	66	85	80
3	306	285	–21	105	130
4	288	328	40	100	155
5	248	248	0	185	115
6	353	448	95	180	190†
7	246	352	106	90	110
8	207	257	50	135	95
9	277	361	84	110	150
10	129	144	15	80	60
11	253	251	–2	125	92
12	254	308	54	150‡	90‡
13	305	365	60	80	65
14	271	287	16	140	215
15	370	408	38	230§	192§
Mean	260	301	41	118	121
Extremes	129	144	–21	80	60
	370	448	106	230	215

*Not included in calculation of mean because no reading available in comfortable room for comparison.

†Values actually higher than indicated here. The rise in pressure extended above phlebomanometer scale and could not be determined.

‡Not utilized in calculation of mean because probable acute pulmonary edema developed in Patient 12 in the cold room, and the usual hepatic pressure could not be applied.

§Not included in calculation of mean because rise in venous pressure extended above phlebomanometer scale and could not be determined.

Pressure over the hepatic area tended to produce a greater rise in venous pressure in the patients with congestive failure than in the normal subjects (Tables II and III, Figs. 1 and 2). After the patients' exposure to the cold atmosphere, the rise tended to be even greater and more readily produced by pressure over the hepatic area. In fact, it was evident that extreme, prolonged pressure would have produced acute exacerbation in the cardiac failure and perhaps even acute pulmonary edema. Because of these possibilities, pressure over the hepatic area was made more gingerly and usually with less force after these patients were cooled.

Venous pressures were recorded in the patients with congestive failure immediately following release of pressure over the hepatic area. There tended to be a small but definite, fall below the level existing before hepatic pressure was applied. This same phenomenon was observed in association with coughing in some subjects.

Arterial Blood Pressure, Pulse Rate, and Respiratory Rate.—Both the normal subjects and the patients with congestive failure, on exposure to the colder en-

vironment, tended to exhibit an increase in systolic as well as diastolic pressure, although this rise was not an absolutely constant observation (Figs. 1 and 2). The pulse and respiratory rates in the normal subjects tended to decrease slightly, whereas these rates in the patients with congestive failure tended to remain essentially unchanged, possibly in part because of digitalization. In the patients with congestive failure, the respiratory rate definitely increased in only one subject (Case 10), who became extremely orthopneic during the period of cooling, necessitating her movement to a warm room. Although 4 subjects became much more dyspneic in the colder environment, no accompanying significant change in respiratory rate was observed.

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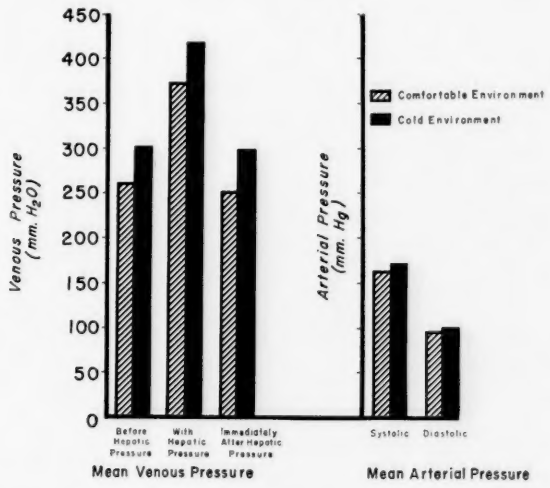

Fig. 2.—Influence of a moderately cold environment on venous pressure in patients with chronic congestive heart failure. The mean venous pressure is shown before and during hepatic pressure in a comfortable, as well as cold, environment for 15 patients with chronic congestive heart failure.

General Reaction.—All *normal subjects* had essentially the same general response to cooling. They gradually became colder until they felt they were about to have a rigor or until they actually experienced one. Except for these sensations, the general reaction was not unusual. The superficial veins became smaller, cutis anserina ("goose flesh") appeared, the surface of the body became cold and cyanotic—all well-known general manifestations of a normal person to a cold environment.

The *patients with congestive heart failure* reacted in the same general manner as the normal subjects except that the jugular veins seemed to become more distended and turgid in the subjects whose venous pressure rose. Four patients became decidedly more breathless, and 2 had to sit erect because of severe orthopnea. These had to be transferred to a warm room after relatively brief exposure to the cold. Although several of these patients seemed to show little objective change in the clinical manifestations of their heart failure, subjectively their breathing was more difficult in the colder room, and they requested transfer to a warmer room for relief.

DISCUSSION

Constriction of the superficial veins of the body, upon acute exposure of the subject for a few minutes to a moderately cold atmosphere, is responsible for, and reflects, a shift of blood from the surface of the body, which acts to conserve the body heat. With constriction of the veins, systemic venous hypertension developed in most of the normal subjects and increased further in most of the patients with chronic congestive heart failure. Since pressure in the median basilic vein probably reflects the pressure in the entire systemic venous system, venous tone must have increased generally, and not merely in the superficial veins, in response to the colder atmosphere. Venomotor tone was definitely increased in the superficial veins of the body.

Increase in venous tone and pressure with sudden chilling of the body may have clinical significance. A patient with venous hypertension and congestive heart failure may experience cardiac or circulatory difficulties and worsening of the cardiac state with a further rise in venous pressure. Four of the 15 patients with congestive failure studied in these experiments exhibited an exacerbation of failure in response to sudden exposure to a colder environment. Their response resembled that of a person who had been running. This worsened cardiac state was quickly relieved by termination of the study and return to a comfortably warm atmosphere. Slow and insidious cooling, on the other hand, may fail to disturb such a subject in congestive failure because of factors of acclimatization still unknown or poorly understood.

The response to sudden chilling may reflect, in part, influences of increased venous tone, venous pressure, and shifts of blood to the lungs; increase in arteriolar and peripheral resistance and increase in load in the left ventricle may have been additional contributing factors. The response may be equivalent to infusion of blood into the veins of a patient with congestive heart failure and venous hypertension, one with impaired cardiac reserve, or one with impending clinical manifestations of failure or myocardial insufficiency who has a resultant excessive increase in pulmonary blood volume and pulmonary venous pressure. This response of the veins and of venous pressure to cooling is important in the management and course of myocardial disease and congestive heart failure. The present studies in a moderately cold environment, as well as previous ones in a hot and humid atmosphere,[1,2] seem to indicate the desirability of a comfortable environment for patients with cardiac disease and congestive heart failure. Obviously, the conditions of an ideal comfortable environment must vary with the degree of physical and mental activity of the patient and the amount of clothing he is wearing.

The well-known clinical observation that a patient with angina pectoris (anginal failure) is more prone to experience anginal pain when he is walking against a cold wind may be explained in part by alterations in venous function. This phenomenon requires further study.

In several subjects, surface temperature of the body and venous pressure were recorded continuously throughout the time of exposure to the cold environment. Venous pressure rose almost immediately after exposure and occasionally declined slightly as exposure continued. Skin temperature slowly declined over

the face, thorax, arms, legs, hands, feet, and tips of the digits as exposure to the cool air continued. The digits became coldest, a plateau never actually being reached for the duration of these studies, which did not exceed sixty minutes.

It is evident from these experiments that the veins of man are not passive vascular tubes but rather participate actively in cardiovascular adjustments to the environment. The mechanism for venous adjustments to chilling is not known but is probably mediated in large part through the sympathetic nervous system. The reciprocal relation of the superficial venous system and the veins deep within the body must play an important role in the adjustment of the venous system to changes in environmental temperature. Should the large central veins or venous reservoirs have high tone and resist further distention with blood, a given cold environment would be expected to increase venous pressure more than if these veins were readily distensible. The sympathetic nervous system, blood volume, local venous axone and baroreceptor reflexes, and humoral factors must all be concerned, in a complexly integrated fashion, with the control of venous tone and venous pressure locally, as well as generally.[14,15]

Increase in arterial blood pressure was probably produced by arteriolar constriction in response to chilling of the surface of the body.[7] The vasoconstrictive response in the superficial arterial system of the body reduced blood flow to the skin and loss of heat.

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SUMMARY

Sudden chilling of the body of normal young men by a moderately cold atmosphere definitely increased venous tone and venous pressure, whereas it tended to increase systolic and diastolic arterial blood pressure and decrease pulse and respiratory rates. The superficial veins of the body constricted greatly. This response is certainly concerned with thermal regulation.

The response of 15 patients with chronic congestive heart failure to sudden exposure to a moderately cold environment was essentially the same as that for the normal subjects. Superficial venous pressure increased, especially in response to pressure over the hepatic area. Four subjects experienced increased dyspnea after several minutes of exposure to the colder environment, 2 seriously enough to necessitate immediate transferral to a warm room. An environment considered comfortable by the subject appears to be most desirable. Acclimatization, physical and mental activity, clothing, and cardiac reserve are among the many factors to be evaluated in selection of the ideal environmental atmosphere.

These experiments indicate the important, and possibly detrimental, influence of sudden cooling of a subject with cardiac disease, a factor worthy of some consideration in therapy. These studies show further that the veins are not passive vascular tubes but rather participate actively in cardiovascular regulatory phenomena.

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REASONS FOR PROLONGED HOSPITAL STAY

A Study of Need for Hospital Care

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As the costs of constructing and operating general hospitals are mounting, efficient utilization of these expensive facilities for medical care is becoming a matter of growing concern. The general hospital will be utilized to the best advantage of the sick, the payment agency, and the community at large if both admission and length of stay are based on the patient's need for services which cannot be rendered at all, or as well, in other types of institutions or in the outpatient clinic, physician's office, or home.

The necessity of efficient utilization of general hospitals has been stressed and various methods for its attainment have been described in the early part of this century by several German authors, especially Grober, Gottstein, and Goldmann.[1] More recently the particular question of the "long-stay" patient has been the subject of investigations in Birmingham, England,[2] Saskatchewan, Canada,[3] Vermont,[4] and Maryland,[5] and the city of New York.[6,7] Cosin[8] has reported on interesting experiments designed to achieve the dual objective of better patient care and best possible utilization of general hospitals.

In Boston, Massachusetts, an investigation into the need for general hospital care and the reasons for prolonged stay in such institutions was undertaken in 1954-1955. It was one of a series of studies designed to develop methods of measuring quality of medical care and of evaluating the adequacy and efficiency of community health services. The methodology and the findings of this study are reported in the subsequent sections.

This investigation was carried out by the United Community Services of Metropolitan Boston in cooperation with the Harvard School of Public Health, and was supported in part by a Research Grant (RG-4045C) from the National Institutes of Health, Public Health Service.

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METHODOLOGY*

Long-stay patients in general hospitals were selected for the study since this group is known to include a number of persons who no longer require active treatment but, nevertheless, remain in the hospital for a variety of reasons. Such patients do not constitute a large proportion of all hospitalized persons, but they account for a relatively large fraction of patient days of care as Rorem,[9] among others, has pointed out.

Thirty days was chosen as a working definition of long-stay on the assumption that, by the end of this period, the medical inventory of the patient should be reasonably complete, and detailed information on clinical status would be available. Use of thirty days as a basis for identifying long-stay is a widespread practice. The National Conference on the Care of the Long-Term Patient defines long-term patients as ". . . those persons suffering from chronic disease or impairments who require a prolonged period of care, that is, who are likely to need or have received care for a continuous period of at least thirty days in a general hospital, or care for a continuous period of more than three months in another institution or at home. . . ."[10] A similar definition has been used in the Vermont and Maryland studies.[4,5] The American Hospital Association regards an average stay of thirty days as the line of demarcation between short-term and long-term hospitals.[11]

In order to test methods under varying circumstances, four hospitals were selected that differed in auspices, types of service provided, and teaching responsibilities. They included two voluntary teaching institutions, a city hospital also used in teaching medical students, and a small voluntary community hospital.

Methods were developed for accumulation of the following three types of data at each of the study hospitals: (1) administrative data concerning admission, case review, discharge policies, and availability of special services for the chronically ill; (2) statistical data concerning certain characteristics of patients discharged in 1953 (the last year for which complete data were available when the study was initiated); (3) case data including information on medical and nursing status and needs.

Classification of Facilities.—The several types of institutional facilities serving a metropolitan community were identified and an effort was made to construct, on the basis of current practice, a system of definitions of function for each type of facility. Included in this initial exploration were: the general hospital, convalescent facility, chronic disease hospital, custodial facility, nursing home, and boarding home or home for the aged.

Tests of the usefulness of these definitions for the grouping of patients indicated that the classification of facilities was not mutually exclusive. Difficulties were encountered in distinguishing between patients requiring active medical care in a chronic disease hospital and those needing such service in a general hospital. Considerable overlapping was found between the functions of the

*Copies of a more complete report on methodology and findings are available on request.

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custodial facility and the nursing home, and it was hard to develop a rational basis for choice between a nursing home and a convalescent home.

Accordingly, the original classification of facilities was abandoned, and a new classification, with appropriate definition of functions, was adopted for the purpose of the study. It includes the following four hypothetical types.

1. *Facility for active medical care:* This facility would provide for intensive and continuous diagnostic, therapeutic, and rehabilitative services requiring the concerted effort of an organized team of highly skilled professional persons and, frequently, the use of highly specialized equipment. It would be equivalent to the inpatient services of general hospitals and chronic disease hospitals with active treatment services.

2. *Facility for extended chronic care:* This facility would be equipped to provide general medical supervision and intensive, or moderately intensive, nursing service for patients with severe or moderate permanent handicaps, who are offered little prospect of rehabilitation under the current status of medical knowledge and do not need active medical treatment. Cases suitable for treatment in such a facility present many social as well as medical problems.[12] At present, such service is provided by so-called custodial institutions and nursing homes.

3. *Facility for intermediate care:* This facility would be designed for patients classified as requiring nursing service and general medical supervision who are, nevertheless, sufficiently active and competent to attend to most of their own daily nonmedical requirements. It would accommodate patients being prepared for elective surgery and convalescents; as well as persons with more prolonged, though not disabling, conditions.

4. *Non-medical facility:* This facility would provide for persons who need shelter and require only general medical supervision, episodic medical care, or no medical service.

This classification of facilities proved to be useful for the purpose of the study. Nevertheless, it is theoretical, and it should not be construed as a recommendation to be followed by individual communities in planning for construction of physical facilities. Responsibility for care of various categories of patients may be distributed in various ways among separate facilities, or it may be vested in specialized divisions of a single facility. In any case, clear definition of the functions of the several units is essential to effective coordination of service.

Patient Characteristics.—In order to relate patient needs to the type of facility best suited for them, a comprehensive classification of patient characteristics and a series of definitions for each characteristic were developed so that all patients could be appropriately classified.* The following characteristics proved to be decisive to proper determination of the facility needed: (1) service requirements for medical and nursing care and rehabilitation; (2) degree of permanent loss of function; and (3) short-term prognosis for life (under two months), moribund patients being considered unsuitable for transfer or discharge.

Additional characteristics were used for classification of patients. They included age, severity of illness, and rehabilitation potential. None of them was

*See Appendix for classification of patient characteristics.

found to be of critical importance to the identification of the facility required by the patient. Social needs were not included in the patient profile, as suitable data were lacking in many instances, and a social inventory of patients could not be carried out as part of the study. This made it impossible to determine whether patients who do not require continued hospital care could be adequately cared for at home. When patients were known to social service departments, pertinent information was obtained with the result that some insight into nonmedical reasons for hospitalization was gained.

Accumulation of Case Data.—A schedule was developed for accumulation of information needed to classify patients according to the several selected characteristics. It contained sections on medical status, services required, and reasons for continued hospitalization. In addition, it provided for space for description of the socioeconomic status. The information was gathered from medical and nursing records, and through interviews with members of the medical, nursing, and social work staffs. Each case record was reviewed by a physician and a nurse in consultation with a social worker, and was classified according to the several characteristics outlined above. The patient profiles were then compared with the definitions of function of the several types of facility. A similar approach to classifying patients according to medical and nursing requirements, as a basis for estimating need for hospitalization, was used by Lowe and McKeown in Birmingham,[2a] although their specific standards differed from those used in this study. Other groups have conducted studies designed to classify patients according to nursing service requirements.[13] There is evidence of need for further studies of this nature.[14]

FINDINGS

The four institutions studied follow widely varying policies in accepting patients. Two (hospitals A and B) maintain special services for the chronically ill; the third one (hospital C) admits chronically ill patients to medical and surgical services as required, but does not maintain specialized services for this group; and the fourth one (hospital D) ordinarily does not admit patients with chronic illness, but directs them to other institutions.

At two of the institutions (hospitals A and C) there is a system of regular review of ward patients by a physician, medical social worker, and nurse. These review procedures are known by different names, including "ward conferences," "medical social ward rounds," or "patient care rounds."

Although all four institutions operate as general hospitals, they differ considerably in their role in the community. It is noteworthy that, despite the absence of over-all community planning for regional integration of hospital facilities, interdependence and a certain degree of specialization of function have developed spontaneously; the larger teaching institutions providing specialized services for certain types of chronically ill patients which the community hospital could not economically provide.

Discharge Study.—Study of a sample of patients discharged in 1953 confirmed findings of other studies with regard to the importance of the problem of the long-stay patient, and the characteristics of these patients. The combined data of

the four institutions indicated that only 6 per cent of the patients remained in the hospital 30 days or longer, but that these patients accounted for almost one-third of the total patient days of care (Table I).

TABLE I. PERCENTAGE DISTRIBUTION OF PATIENTS AND DAYS OF CARE BY LENGTH OF STAY IN FOUR STUDY HOSPITALS, 1953

ALL HOSPITALS	ALL PATIENTS	LENGTH OF STAY IN DAYS						
		0-9	10-19	20-29	30-39	40-49	50-59	60+
Per cent of patients	100	68	16	10	3	1	1	1
Per cent of days	100	28	19	21	8	5	5	14

Average length of stay, per cent of patients hospitalized 30 days or more, and per cent of days of care for those patients varied widely among the four hospitals due to differences in their policies and services (Table II). Average stay was longer at the two institutions maintaining special facilities for the chronically ill.

TABLE II. AVERAGE LENGTH OF STAY OF ALL PATIENTS AND PER CENT OF DAYS OF CARE OF LONG-STAY PATIENTS HOSPITALIZED THIRTY DAYS OR MORE ACCORDING TO HOSPITAL

HOSPITAL	AVERAGE STAY OF ALL PATIENTS	30 DAYS OR MORE (PER CENT)	
		PATIENTS	DAYS' CARE
All Hospitals	11.1	6	32
"A"	11.3	9	34
"B"	12.3	7	35
"C"	8.4	3	17
"D"	7.1	2	13

In general, the long-stay group contains a substantially larger proportion of elderly patients than does the short-stay group. Persons 65 years of age and over constituted 30 per cent of the long-stay patients, compared with 16 per cent of those hospitalized for less than 30 days. Three categories of illness (tumors, cardiovascular diseases, and injuries) accounted for 52 per cent of the long-stay cases, but for only slightly over 30 per cent of cases hospitalized for less than 30 days. Significantly, a higher proportion of long-stay patients depend on the community and the hospital for payment of the hospital bill than is true of the short-stay group.

Study of Individual Cases.—There were 369 long-stay cases at the four institutions. One-third samples of all long-stay patients (stratified according to length of stay) at hospitals A and B were studied, while all long-stay patients in the other institutions were reviewed. At the time of the study, 19.5 per cent of the patients in the four hospitals had been hospitalized for 30 days or more.

The per cent in each hospital again reflected the effect of admission and discharge policies. Consistent with the findings of the study of discharges in 1953, tumors, cardiovascular disease cases, and injuries accounted for 59 per cent of the long-stay group.

The distribution by length of stay of long-stay patients at the time of the study in the four hospitals is shown in Table III. The effect of hospital admission policies and services is evident. While 5 per cent of the patients in hospital C, and none in hospital D had been hospitalized for 90 days or more, 29 per cent and 22 per cent of the patients in hospitals A and B, respectively, had been hospitalized for that length of time. In comparing average length of stay in general hospitals, due consideration must be given to variation in policies and services maintained.

TABLE III. PERCENTAGE DISTRIBUTION OF LONG-STAY CASES IN STUDY HOSPITALS ACCORDING TO LENGTH OF STAY AT TIME OF STUDY

LENGTH OF STAY IN DAYS	ALL HOSPITALS	HOSPITAL			
		"A"	"B"	"C"	"D"
All Cases	100	100	100	100	100
30–59	57	46	58	84	67
60–89	21	25	20	11	33
90–119	8	11	8	5	0
120–149	7	7	7	0	0
150–179	4	11	2	0	0
180+	3	0	5	0	0

According to the criteria for evaluating patients' needs, it was estimated by us that *about 56 per cent of the patients required active hospital care and 42 per cent did not require it, but needed other types of care.* In 2 per cent of all cases no rating could be made (Table IV). This distribution varied among the several hospitals.

TABLE IV. PERCENTAGE DISTRIBUTION OF LONG-STAY CASES IN STUDY HOSPITALS ACCORDING TO MEDICAL FACILITY NEEDED*

FACILITY NEEDED*	ALL HOSPITALS	HOSPITAL			
		"A"	"B"	"C"	"D"
All Cases	100	100	100	100	100
Active hospital	56	71	51	63	33
Long-term chronic	16	4	19	21	33
Intermediate care	12	7	14	5	0
Nonmedical facility	14	18	14	11	17
Not ratable	2	0	2	0	17

*In our judgment after the survey.

All evidence indicated a direct relationship between the activity of the social service department, and the per cent of long-stay cases judged to require active hospital care.

No relationship was found between length of stay and the need for active hospital care. Of those patients who had been in the hospital from 30 to 119

days, 56 per cent were in need of active hospital care, compared with 53 per cent of those hospitalized for more than 120 days.

TABLE V. PER CENT OF PATIENTS REQUIRING ACTIVE HOSPITAL CARE ACCORDING TO LENGTH OF STAY AT THE TIME OF THE STUDY

LENGTH OF STAY IN DAYS	ALL PATIENTS	REQUIRING ACTIVE CARE	
		NUMBER	PER CENT
All Cases	369	206	56
30– 59	210	125	60
60– 89	77	36	47
90–119	31	18	58
120–149	24	12	50
150–170	15	6	40
180+	12	9	75

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The review of case data made it clear that it would be unrealistic to classify the patients' institutional requirements according to length of stay or chronicity of illness. Similarly, the age of the patient showed little relationship to the type of service required. Of patients under 45 years of age, it was estimated that 60 per cent needed the services of an active facility, while 54 per cent of those 45 years of age and over required this form of service. Nevertheless, the median ages of those judged to need services of a long-term chronic facility, and of those requiring an intermediate facility were higher, and the median age of those needing a nonmedical facility was lower, than that of all long-stay patients.

Table VI shows the distribution of patients assigned to the several types of facility according to the amount of medical service required. This table reflects the criteria adopted for the study. While 93 per cent of patients considered to need active hospital care required active medical care, none of the patients assigned to other types of facility required such service. The remaining 7 per cent of the patients did not require active medical care, but were assigned to an active facility because of the need for active rehabilitation. Active medical care was defined as the constant availability of a physician's services, with at least one medical visit a day; need for a major surgical procedure; or need for diagnostic services requiring an institutional setting.

TABLE VI. PERCENTAGE DISTRIBUTION BY NEED FOR MEDICAL SERVICE OF LONG-STAY CASES CLASSIFIED ACCORDING TO TYPE OF FACILITY REQUIRED

NEED FOR MEDICAL SERVICE*	ALL FACILITIES	TYPE OF FACILITY			
		ACTIVE HOSP.	LONG-TERM CHRONIC	INTER-MEDIATE	NON-MEDICAL
All Cases	100†	100	100	100	100
None or episodic care	8	0	5	14	37
Regular medical supervision	38	7	95	86	63
Active medical care	52	93	0	0	0

*See appendix for description of type of medical care.
†Two per cent of the cases were not ratable because of lack of essential information.

The 206 patients who were considered to need active hospital care remained in the hospital for a variety of medical reasons, as shown in Table VII.

TABLE VII

MEDICAL REASONS FOR CONTINUED STAY	NUMBER OF CASES	PER CENT
All Cases	206	100
Diagnosis	22	11
Surgery	115	56
Medical treatment and observation	41	20
Rehabilitation	18	9
Psychiatric observation	7	3
Isolation	3	1

About 60 per cent of the patients with a surgical indication for continued stay were being prepared for major surgery, including restorative procedures following injury, skin grafting, second stage procedures, and for operations decided upon after the failure of conservative methods. In certain instances, hospital care was prolonged only because there had been inordinate delay in scheduling necessary surgery. The remainder of the cases in the group were recovering from major surgery.

Patients remaining for medical reasons included some who were treated for complications, such as bedsores, rather than for care of the condition for which they had been admitted. It is likely that better nursing care would have prevented many of these complications.

Of the 156 patients not requiring continued active hospital care, 58 (37 per cent) were not known to the social service department, so that there was no information on the social or nonmedical factors responsible for continued hospital stay. Of the patients for whom data were available, 38 per cent remained because of unsuitability of the home; 28 per cent because of family reluctance to accept the patient; and 25 per cent because of lack of other suitable facilities in the community. Nine per cent stayed on for research purposes. It is recognized that research constitutes a proper indication for continued hospital care in a teaching institution. However, this group of patients was included among those not requiring hospital care in accordance with the criteria adopted for the study.

Hospitals encountered difficulties in placing mentally retarded children; children with malformations, whose families could not care for them; alcoholics; and patients with epilepsy. Often, there were months of delay in transferring patients to other facilities because of long waiting lists. Frequently, it was almost impossible to find nursing homes suitable to meet the needs of aged persons at a price they could afford, or public agencies were willing to pay. There is evidently a need for some facility such as the "halfway house" in England for those patients who require only limited medical and nursing service, but who must be kept under observation.[15]

DISCUSSION

Admission to, and length of stay in, the hospital are attributable to a combination of social as well as medical factors. While most patients are admitted

to general hospitals because of specific medical needs only, a good many seek admission, or remain in the hospital, for socioeconomic and psychologic reasons as well. Often medical needs are overshadowed by the need for physical or psychologic shelter. Many persons who no longer require general hospital care, but who do need care in a nursing home or custodial facility or require some other form of service or assistance, must be kept in the hospital at public expense because of difficulties in finding a suitable place or service at reasonable cost.

The economic implications of inappropriate placement of the patient in a general hospital, or of stay longer than medically indicated, are grave indeed. Unnecessary hospitalization is costly not only in terms of dollars spent, but in terms of diminution of resources and services for those who urgently need the specialized services of the general hospital. It aggravates the shortage of beds, and may well raise a serious staffing problem in view of current, and probably growing, shortages of hospital personnel in a number of categories.

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Equally important, but less frequently taken into account, is the impact of a long hospital stay on the patient. It can easily have harmful effects on the patient, his relationships with his family, the community, and his ability to readjust to the life in the community upon his return.

It is recognized that many patients are dependent on continued institutional care after their immediate medical needs have been met. In the interest of both patient welfare and economy such care should be provided in an institution assuring the patient maximum independence compatible with his condition, and affording the closest resemblance to a home environment. Deficiencies in the number and quality of institutions for long-term care of the sick, of homelike institutions for those who need shelter and aid, and of organized programs of home care are drawbacks to efficient utilization of general hospitals. They must, and can, be eliminated by development of the various types of physical facilities and of programs providing for medical care in the patient's own home where indicated.

The general hospital and related medical institutions have come to provide a large variety, and many combinations, of specialized services to meet medical needs. In them, thousands of judgments concerning admission, discharge, and transfer of patients are made each day. Yet, there are no generally accepted criteria to serve as guides, because of the complexity of factors on which judgments are based, and because of changes in the relative values of the several factors with changes in medical science and practice, in economics, and in social philosophy. This study has been designed as a first approach to the problem of developing and testing criteria. It is hoped that it will encourage similar studies elsewhere, so that ultimately generally applicable criteria evolve.

Such criteria would be useful to general hospitals in classifying their patients according to need, in grouping patients with similar needs, and in reviewing their policies, or in conducting periodic inventories. They would be valuable in conducting community-wide studies into the efficiency of utilization of hospitals and related facilities. Studies of this type would reveal not only the extent to which patients are institutionalized in a particular facility without requiring

its services; but could, at the same time, determine the reasons for inappropriate placement, and measure the relative importance of the several factors involved.

Furthermore, criteria for selection of patients for the several types of medical facility would provide a sounder basis for estimates of future bed requirements, in contrast to the present highly empirical (and often inadequate) methods of estimating needs for general and chronic disease hospitals and related facilities.

Although the concepts of the function of general hospitals and other medical facilities change with time, a working definition based on reasonable interpretation of current practice should be adopted for purposes of planning. With such definition of functions, it would be possible to develop and apply criteria in sample studies in the several types of medical facility in the community, and to estimate the distribution of needed beds provided that the sick are placed in specialized facilities according to their particular requirements. Such data, combined with information on trends in utilization, should give a more precise picture of the foreseeable demand for care in the several types of medical institutions, and guide community action in building the necessary facilities.

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SUMMARY

1. In four general hospitals in Boston, Massachusetts, a study of patients staying 30 days or longer was made to determine the reasons for their prolonged hospitalization and to define the factors affecting hospital utilization. It included an analysis of a sample of patients discharged in 1953 and a detailed review, by a team of professional persons, of a sample of 369 "long-stay" patients in the four hospitals in the year 1954.

2. Each of the long-stay patients in the sample was evaluated as to specific requirements for service on the basis of specially developed criteria including a list of facilities performing different functions and a list of patient characteristics indicating need for service in one of the various types of facility.

3. As the discharge study showed, only about 6 per cent of all patients remained in the hospital 30 days or longer, but this group accounted for almost one-third of the total patient days rendered.

4. The case study revealed that about 56 per cent of the long-stay patients required continuing active treatment in the hospital, while 42 per cent did not require it, although many of them needed other types of care.

5. The main reasons for keeping patients in the hospital despite absence of need for continued active treatment were unsuitability of the patient's home, reluctance of the family to accept the patient, and lack of other facilities and services—such as institutions for long-term care of the sick, homelike institutions for those who need shelter and aid, and organized programs of home care.

6. The long-stay group contained a relatively large proportion of elderly people and of patients with tumors, cardiovascular diseases, and injuries.

7. The methodology developed for this study lends itself to wider application. It is believed that the methods developed may be useful in making estimates of future need for general hospital beds, and for the various types of physical facilities and services required for the humane, efficient, and economical care of patients with prolonged illness.

8. The findings indicate the importance of availability and effective coordination of various types of facilities for medical care, and other services for the sick and infirm in the community.

APPENDIX

Standards for Classifying Patient Characteristics

I. *Service Requirements.*
   A. No special service, or only episodic service required.
   B. General supervision.
      1. *Medical:* less than one visit per day.
      2. *Nursing:* less than two hours of nursing care by a registered nurse per day with maximum total of three hours of nursing care required.
      3. *Rehabilitation:* less than three and one-half hours of rehabilitation service per day.
   C. Active care.
      1. *Medical:* Constant availability of services of physician, or at least one visit per day.
         Major surgical procedure.
         Diagnosis involving such procedures as require an institutional setting (i.e., angiography, encephalography, cardiac catheterization, or skilled observation).
      2. *Nursing:* More than two hours of care of a registered nurse per day, or a total of more than three hours of nursing service per day.
      3. *Rehabilitation:* More than one-half day of rehabilitation service per day.

II. *Degree of Permanent Loss of Function.*
   A. Unlimited ability to pursue activities normal for the age and sex of the individual.
   B. Limited ability to work at usual or changed occupation, or to pursue normal activities.
   C. Able to carry out activities of daily living, but unable to work or adjust independently.
   D. Limited ability to carry out activities of daily living.
   E. Complete dependence, unable to carry out important activities of daily living.
   F. Undetermined.

III. *Short-Term Prognosis (under two months).*
   A. Good.
   B. Fair.
   C. Poor.
   D. Hopeless.
   E. Moribund.
   F. Undetermined.

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EXPERIENCE IN PHYSICAL MEDICINE AND REHABILITATION ON A HOME CARE PROGRAM

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THE concept of home care as a service for the chronically ill has become well established since the first trial at Montefiore Hospital in 1947. Recent publications have described the role of home care in the management of patients[1,2] with rheumatic heart disease and cancer. This paper deals with the experience in the area of physical medicine and rehabilitation during the five years the author was associated with the Montefiore Home Care Program.

From its inception the Montefiore Program has included the services considered basic to physical medicine and rehabilitation. These include an attending physiatrist, a physical therapist, occupational therapist, social worker, and visiting nurse service. Services in other medical specialties are available on a consultation basis. The attending physiatrist is also a member of the hospital physical medicine and rehabilitation services so that continuity of patient care is easily maintained.

The major areas of consideration in clinical care are: (1) selection of patients, (2) type of patient, (3) admission to the program, (4) treatment on program, and (5) follow-up.

Selection of Patients.—Patients referred from within the hospital or by other hospitals and private physicians are seen for medical approval by an attending physician from Home Care. Patients whose problems are primarily in the realm of physical medicine and rehabilitation are evaluated by a physiatrist. If medically approved, the patient, family, and home are evaluated by the social worker, because careful social evaluation is necessary to assure successful management at home. Experience has shown that the medical problem has seldom been a cause for rejection in cases referred for rehabilitation.

Type Case.—Cases referred represent the average diagnostic problems seen in any inpatient physical medicine and rehabilitation service, but not necessarily in the same order of frequency. During the 5-year period covered by this report 122 new patients were treated by the physical medicine and rehabilitation service in the following categories: hemiplegia, 20; rheumatoid arthritis, 16; amputees, 15; fractures, 9; paraplegia, 5; muscular dystrophy, 4; and polyneuritis, 3.

The remainder of 50 represented patients carried on the program for other medical reasons and received symptomatic physical medicine treatment for bursitis, neuritis, back pain, etc.

These 72 rehabilitation cases represent 12 per cent of the total Home Care case load during this 5-year period.

Most of these patients had started their rehabilitation while in the hospital and were discharged home weeks to months before their program was completed.

Admission to the Program.—Prior to discharge from the hospital, a physical medicine and rehabilitation prescription is written, and the needs of the patient for special equipment (wheel chairs, braces, etc.) are determined and provided for. Shortly after the patient arrives home, a joint visit of the physiatrist and physical therapist is made. At this time the goals are re-evaluated and, if indicated, the prescription changed. Arrangements are made to have a responsible member of the family at home during this visit so that the prescription and goals are well understood by both patient and family.

Treatments.—Physical therapy treatment is provided by the physical therapist varying in frequency from twice daily to twice weekly. In rehabilitation cases, treatment consisted mainly of passive, active, and resistive exercises and ambulation training. Treatment sessions are 30 minutes to one hour in duration. Where indicated, additional therapy time is provided through the visiting nurse service. Occupational therapy is available to all patients and is provided mainly on a diversional basis.

Follow-up.—Visits to the patient's home by the attending physiatrist are made either weekly or not less than every other week. At such time the physical therapist is present and, when indicated, is accompanied by the social worker and/or nurse. Prescriptions and goals are reviewed and necessary changes made.

All cases are reviewed briefly by the attending physiatrist and the entire Home Care staff at a conference every 2 or 3 weeks. Complex problems are presented to the Home Care conference with the director of Home Care presiding.

Experience with three different disabilities will illustrate the rehabilitation potential in the home.

CASE 1.—A 42-year-old woman with rheumatoid arthritis of 20 years' duration was admitted to the program because she could not come in for clinic care. There was significant involvement of all the major joints, but activity was at a low grade. At the time of the first home visit, the patient was found in bed. She had to be carried down the steps and could only walk the few steps to the toilet with great difficulty. There was marked depression with frequent weeping, and she constantly demanded analgesia and sedation. Massage and range of motion exercises were prescribed prior to ambulation training. Treatment was given on a daily basis. Progress was very slow and discouraging. The family tensions produced by the patient's physical and emotional needs required the close attention of the social worker. Further support of the home situation was provided by the visiting nurse. This concentrated service of physician, physical therapist, social worker, and visiting nurse slowly produced the desired results. The patient and family became adjusted to the complex problems, and there was an upturn in her condition. Progress became quite rapid; she walked about freely and even did her own shopping. She now reports to the hospital regularly for treatment.

Comment.—This case illustrates the feasibility of bringing the teamwork concept of rehabilitation into the home. Further, the complex adjustment between family and patient probably could not have been resolved without the follow-up offered by the program.

CASE 2.—A 26-year-old woman, with paraplegia of 4 years' duration secondary to trauma, was admitted to the Home Care Program after 7 months of treatment in the hospital. Discharge home was arranged as soon as the principles of ambulation on crutches had been mastered. She still could not get out of a chair or sit down alone and also could not climb steps. Daily visits by the physical therapist were instituted. The patient made rapid progress at home and within 3 months had almost achieved complete independence.

Comment.—Experience has shown that the paraplegic not infrequently shows a regression in physical capacities after discharge from the rehabilitation center. This patient made significant progress at home and actually completed her rehabilitation program while at home.

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CASE 3.—A 63-year-old woman with diabetes was discharged home one month after left below-knee amputation. The patient's husband, who suffered from cardiac disease, could not manage alone at home, and hospitalization was suggested. The patient insisted on returning home to care for her husband even though she could not ambulate on crutches. Both the patient and her husband were placed on the program. His cardiac condition was controlled rapidly, and he was discharged for further care to the clinic. She was put on an exercise program and stump bandaging. Crutch-walking was managed with some difficulty, and she carried out most of her household duties from the wheel chair. Help was provided by housekeeping service. After the final fitting of her limb, gait training was rapidly successful, and she was discharged to the clinic for further follow-up.

Comment.—This case illustrates the well-known influence of emotional factors on the rehabilitation program. If her care had been continued in the hospital, this patient's anxiety over her husband's illness would undoubtedly have delayed her rehabilitation. She had been considered an uncooperative patient in the hospital and was fully cooperative at home. Home Care helped in resolving her problem and enabled her to participate in rehabilitation.

DISCUSSION

Medical rehabilitation utilizes a number of professional disciplines and significant quantities of equipment. Such an organization is usually possible only in hospitals or large outpatient departments. For this reason it was first thought that rehabilitation at home would consist of maintenance therapy. Actual experience over a 5-year period supports the present attitude that home care rehabilitation is an active service which can bring effectively into the home all disciplines required for rehabilitation. Further, there are distinct advantages to home care rehabilitation and no significant disadvantages. Some of the advantages are:

1. *Maintaining Progress and Activity.*—Hospital-attained goals are easily continued into the home. Without home care, it is usual to find that the rehabilitation patient, when returned home, suffers some loss of activity compared to that achieved in the hospital.

2. *Transition From Hospital to Home.*—The prolonged removal of the patient from the family which is necessitated by the hospital rehabilitation program frequently creates one of the most important problems faced in rehabilitation. The patient and family may find difficulty in making the necessary adjustments on his return to the home environment. It is in this period that the hospital program offers little or no support. Some cases of rehabilitation failure necessitating return to the hospital can be traced to lack of support during this critical period. With home care, the transition takes place while the patient is on the active program. All the services are available to deal with problems as they arise. The additional advantage is provided by the fact that in most cases members of the family can be instructed to carry out simple procedures such as exercise, stretching for range of motion, ambulation with crutches, and self-care training. This further extends the therapeutic time and provides a positive contact between the patient and the family. In addition to emotional problems, home care also is prepared to cope with needed changes in the physical facilities at home which were not anticipated while the patient was in the hospital. Also, the rehabilitation prescription on home care tends to be more adjusted to the patient's individual needs as opposed to the standardized organization of the hospital program. This factor enhances the patient's participation in rehabilitation. He is further encouraged by being able to apply the newly achieved skills to improved functioning in the home.

Though this program has been described in relation to a large hospital organization in a large city, the principles involved can be applied to almost any community. By using community resources which are presently generally available, a family physician could carry out a major part of rehabilitation in the home. In consultation with the physiatrist, and with the help of the family, public health or visiting nurse, physical therapist, and the State Division of Vocational Rehabilitation, he could bring to his patient much of the services of modern rehabilitation. Further, he is in the best position to be sensitive to the many social and emotional problems which the disabled encounter. Thus, the rehabilitation process can be centered in the home with all the favorable aspects described above. Hospitalization in the rehabilitation center could be for brief periods of evaluation and intensive therapy. The need for such a program is also made apparent by the widespread lack of adequate rehabilitation facilities and the increasing problem of chronic disease. Since adequate hospital facilities or personnel will not be available in the foreseeable future, this type of home management of the disabled becomes a matter of medical necessity.

Besides offering better care at home for patients, such a program also affords an opportunity for teaching. Medical students and residents can be alerted to the role of the physician in mobilizing and utilizing the complex services which go into the care of the chronically ill patient. The program also provides practical experience in the appreciation of the social, emotional, and economic factors which play such a large role in the management of the chronically ill or disabled patient. This type of experience is not readily available in the inpatient type of training center and could be utilized for medical education at the undergraduate and graduate levels. Rehabilitation home care can thus provide a significant clinical

and teaching function which can be an integral part of or a supplement to in-patient hospital care.

SUMMARY

Home care rehabilitation has proved to be a practical way of reducing hospital stay and assuring proper adjustment to the community in selected cases. Experience with a large group of patients over a 5-year period encourages the viewpoint that this type of service should be part of the over-all rehabilitation program available to the handicapped patient.

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Review

THE KVEIM REACTION IN SARCOIDOSIS

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INTRODUCTION

SARCOIDOSIS, once considered to be a rare and unusual disease of primary interest to the dermatologist, is now recognized as a disseminated process with many regional manifestations. Although knowledge of the fundamental nature and pathogenesis of this disease remains virtually as vestigial as it was thirty years ago, advances have been made in the delineation of its clinical picture. Physicians now realize that the differential diagnosis between sarcoidosis and other disseminated conditions is often exceedingly difficult and that sarcoidosis progresses and regresses irregularly, sometimes with relatively long periods of apparent clinical inactivity. More particularly, we have come to realize that neither the clinical nor the histologic manifestations of sarcoidosis are necessarily pathognomonic. It is not surprising, therefore, that considerable interest should have been aroused when Kveim,[1] in 1941, described an unusual and previously unrecognized cutaneous reaction which promised to be of some use as a diagnostic aid in patients with sarcoidosis.

Kveim noted that following the intracutaneous injection of a heated sarcoid lymph node suspension, 12 of 13 patients with sarcoidosis developed a small indolent papule at the test site within a period of 9 days to 4 weeks. This delayed papular reaction was distinctive in that it usually required weeks to attain its maximum size and then remained visible for many months thereafter. Moreover, if the papule was later excised, it showed a histologic structure resembling that of naturally occurring sarcoid. Control injections of Frei antigen and old tuberculin in the same patients produced no comparable response; and the sarcoid lymph node suspension yielded no such persistent papular reaction when injected intracutaneously into persons with syphilis or lupus vulgaris. Kveim, therefore, believed that this cutaneous reaction was specific for sarcoidosis and theorized that the response might be based on an allergic mechanism.

Prior to the publication of these results, Williams and Nickerson,[2] in 1935, described a cutaneous reaction in sarcoidosis which, in some respects, appears to have been similar to that reported by Kveim. These workers used a saline suspension of cutaneous sarcoid tissue to test 4 patients with sarcoidosis and 4

normal control subjects. Within 24 to 36 hours after the intracutaneous injection of this suspension, Williams and Nickerson observed evanescent reaction papules which lasted approximately a week in the patients with sarcoidosis. No similar results were noted in the 4 control patients. The reactions obtained in the patients with sarcoidosis were described as transient, since none lasted more than 8 days. No mention was made of a delayed response after the initial inflammatory reaction had subsided, nor of any unusual persistence of the experimental lesions—features which are distinctive and characteristic of the typical Kveim reaction. The histology of the evanescent reaction papules obtained by Williams and Nickerson was not studied.

In retrospect, intracutaneous reactions of the type described by Williams and Nickerson would now be considered to be irritant responses of no particular significance because of their brief duration. Subsequently, Nickerson used a suspension of sarcoid spleen tissue as antigen for intracutaneous testing and is said to have noted histologically sarcoid-like granulomatous changes at the test site after biopsy of the reaction papule.[3] In 1940, Harrell[4] attempted to confirm the skin test results reported by Williams and Nickerson, but was not successful. Harrell used suspensions of sarcoid lymph nodes as antigen, prepared according to the method of Williams and Nickerson. Suspensions of tissue from 3 patients were studied. One preparation gave "questionably positive" reactions in 3 patients with sarcoidosis following intracutaneous administration; the other two yielded "completely negative" results in 4 patients. Harrell suggested that his failure to duplicate the results of Williams and Nickerson might be due to the use of lymph node tissue in place of skin as a source of antigen. In the light of present knowledge, this reason would hardly appear to be valid since it is now generally agreed that sarcoid lymph node tissue, for the most part, is superior to cutaneous tissue as a source of Kveim antigen.

Since the publication of Kveim's initial report, a number of studies on the diagnostic usefulness and specificity of the Kveim reaction has appeared.[5-23] Although the results of these studies have not been in complete agreement, and have been subject to individual interpretations at variance with those originally proposed, most investigators have found that the specificity of the Kveim reaction is high and that positive tests in diseases other than sarcoidosis, or in normal individuals, are not common. Noteworthy exceptions to these generally favorable findings are the recent reports of Sones, Israel, and their associates[24,25] who have found the Kveim reaction to be essentially without specificity. These curiously adverse findings remain as yet unexplained. It is not clear whether the failure of these workers to corroborate the specificity of the Kveim reaction was due to deficiencies in their antigens or in their reading of the tests. In any event, while the Kveim test admittedly has some serious limitations as a diagnostic tool, most investigators have found it to be a useful confirmatory aid in sarcoidosis, especially when tissues from involved organs are not readily available for biopsy.

PREPARATION OF KVEIM ANTIGEN

Kveim antigen is prepared from human sarcoid tissue. Any tissue showing the histologic characteristics of sarcoid may presumably be used as a source of

antigen, but experience has shown that the best testing suspensions are derived from lymph nodes or spleen. For mechanical reasons, it is difficult to prepare satisfactory Kveim antigens from cutaneous sarcoid tissue and there is some evidence to suggest that such suspensions are less active than those made from lymph nodes or spleen.[1,6,20,23] Sarcoid tonsillar tissue has not been used extensively as a source of Kveim antigen. Putkonen,[6] and Danbolt[14] have found that antigens prepared from affected tonsils are apt to cause relatively more nonspecific irritative reactions and fewer characteristic positive tests.

Prior to the preparation of the Kveim suspension, portions of the sarcoid source tissue are examined histologically. Acid-fast stains, as well as cultures and animal inoculations for *M. tuberculosis*, are done. Cultures for fungi are also made. If the tissue shows the histologic characteristics of sarcoid and if there is no significant microbial involvement, the material is ready for processing. Under sterile precautions, the sarcoid tissue is weighed and then ground with physiologic saline in a sterile mortar or in a mechanical blender. Sufficient saline is added to give a final dilution of about 1:10 by wet weight of tissue. Sand or other abrasive materials must not be used in the grinding process. Although the resulting suspension may be strained through wide-mesh gauze to free it from the largest shreds of tissue, it is probably preferable merely to allow it to stand for a few minutes. This permits the larger tissue particles to settle and to be discarded without introducing the possibility of contaminating the antigen with fragments of cotton.

The relatively opaque tissue suspension is decanted and heated in a water bath at 56° to 60° C. for 2 hours on 2 successive days. Anaerobic and aerobic cultures are made to insure sterility. If no microbial contamination is present, phenol may be added as a preservative in a final concentration of 0.25 to 0.5 per cent, and the tissue suspension stored in rubber-capped vials at 4° C.

In its final form, the properly prepared Kveim suspension is quite opaque and contains grossly particulate tissue fragments in its sediment. Thus prepared, Kveim antigen is relatively heat stable since it can withstand boiling for 20 to 30 minutes with only partial loss of potency.[6,7,14,21] The active fraction of the antigen is not water-soluble or ether-soluble in the cold.[14] Indeed, Rogers and Haserick[21] suggest that extraction of the antigen with ether may actually enhance the reactivity of the washed residual suspension. These investigators washed regular Kveim antigen five times with ether and discarded the ether-soluble fractions. The remaining suspension was then not only capable of eliciting essentially the same reaction as regular antigen, but the papules were larger and the histologic reaction appeared to be quantitatively greater. On the other hand, Nelson,[26] in a series of unpublished experiments, found that repeated extractions of regular Kveim antigen with a combination of hot organic solvents (boiling alcohol, ether, acetone, and petroleum ether, in succession) destroyed the reactivity of the residual suspension. Apparently, harsh treatment of this type, designed to disrupt lipoprotein linkages, will destroy the potency of the residual suspension and permit at least a portion of the Kveim reactivity to pass into the lipid-extractable fractions. Extracts obtained in this way, when combined and evaporated to dryness, yielded material which could be resuspended in saline with difficulty. This suspension occasionally produced

suggestive Kveim responses when injected intracutaneously into highly reactive patients with sarcoidosis. Such responses, however, were quite irregular. Moreover, attempts to restore full Kveim antigenicity by combining the extracted residue with the lipid-extractable fractions were generally unsuccessful. These data suggest that the reactivity of Kveim antigen depends, at least to some extent, on intact lipoprotein linkages and that measures which tend to disrupt these linkages will impair the potency of the antigen.

The active fraction of Kveim antigen does not pass through Berkefeld or Seitz filters[6,14] but is present in detectable but reduced amounts in the opalescent supernatant portion of suspensions centrifuged at 2,500 r. p. m. for 1 hour. With ultracentrifugation at speeds of 30,000 r. p. m., all particulate matter is removed the clear supernatant layer is then incapable of eliciting a Kveim reaction.[21]

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In view of the crude nature of the suspension used in the Kveim test, standardization of the specificity and reactivity of each lot of antigen is not easy. Since there is no way of determining the potency or specificity of Kveim suspensions without human bio-assay, each lot of Kveim antigen must be tested for reactivity and specificity in normal individuals, in patients with active sarcoidosis, and in patients with diseases other than sarcoidosis, before the material can be used for diagnostic purposes. Moreover, these tests for reactivity and specificity must be repeated at intervals during the shelf life of the antigen.

Some suspensions prepared from histologically typical sarcoid tissue may be totally inert when tested. Other antigens prepared from comparable tissue sources by the same technique have been found to be quite nonspecific in that they yield papular reactions in virtually all volunteers in whom the material is injected and tend to cause irritative tissue responses which interfere with the gross and microscopic reading of the test. Other antigenic preparations prove to be satisfactory for a time, only to lose either specificity or reactivity on storage. Some antigens remain active and specific for years; others deteriorate relatively soon and must be discarded. Active suspensions are not all equally potent and it is virtually impossible to predict which preparations will retain their reactivity and specificity longest. Siltzbach and Ehrlich[20] found that lymph node suspensions were no more potent than splenic suspensions but they appeared to retain their potency and specificity longer. On the other hand, Nelson and Schwimmer[23] have prepared a Kveim antigen from splenic tissue which has retained its potency and specificity for 7 years.

The difficulty in obtaining a regular supply of human sarcoid tissue, the lack of susceptible animals which respond to the test suspension, and the inability to isolate the active fraction of the Kveim antigen in chemically pure form, all contribute to the obvious drawbacks of the Kveim test. The difficulty in standardizing Kveim antigen, and the necessity for evaluating the potency and specificity of each particular lot of antigen at frequent intervals if it is to be used in a skin-testing procedure of this type, cannot be over emphasized. Nevertheless, in spite of these drawbacks, the consensus seems to be that the Kveim test has some usefulness as a diagnostic and, possibly, a prognostic tool. Moreover, since the Kveim reaction is in essence a reproduction of a sarcoid lesion in situ, further investigations of its evolution and behavior may ultimately be important in shedding some needed light on the problem of the pathogenesis of the naturally occurring disease.

TECHNIQUE OF THE INTRACUTANEOUS KVEIM TEST

The Kveim test consists of the intradermal injection of 0.1 to 0.2 cc. of the Kveim suspension into the flexor aspect of the forearm. Since the suspension settles on standing, it should be shaken well to disperse the sediment before the injection is made. The suspension is injected into the skin as superficially as possible in the manner of a Mantoux test, using a tuberculin syringe and a needle of sufficiently large bore to permit free passage of the tissue shreds in the test suspension. The bore of the needle used will be determined by the size of the particulate matter in the Kveim suspension. With some antigens, 24- or 25-gauge needles may be used; with others, a 22-gauge needle may be necessary. The injection should be made as superficially as possible into the skin. If the injection is given too deep in the dermis, a positive test may appear merely as a palpable infiltration, without the development of a visible papule. Such reactions are difficult to read clinically and increase the difficulty of interpreting the test. After the injection, the test site is marked off by measuring its distance from the distal crease of the wrist. This affords a readily identifiable landmark for charting the test site.

For several days after the injection, an area of inflammation is present at the test site. This occurs in virtually all subjects and presumably is due to the trauma of injection. In a negative test, this inflammatory response subsides within a week or 2. In a positive test, a violaceous papule usually appears within 2 to 3 weeks and then begins to grow slowly. It commonly reaches a maximum size in about 6 to 8 weeks, and usually attains a diameter ranging from 3 to 10 mm. Occasionally, in highly reactive patients with sarcoidosis, the Kveim papule may reach a diameter of 15 to 20 mm. Ordinarily, the papule in a positive test will then remain stationary for many months, without ulceration, and then will fade and shrink, leaving a brown pigmentation. In some instances, a positive reaction may be sufficiently intense to cause superficial tissue breakdown and central ulceration which may require many months to heal.

Although the usual typical Kveim papule is well formed by 6 to 8 weeks, we have found lesions developing at the test site as late as 18 months after injection of the antigen. These reactions are usually seen in patients who are tested during a period of clinical remission and who later develop a recrudescence of active disease. Kveim responses with a very long latent period, as well as unusual persistence, have been observed by others. Putkonen[27] reported a "positive Kveim's reaction" which developed at the test site 5 years after injection of the antigen, and Møller[28] has cited a case of sarcoidosis with Kveim reactions which persisted for 9 years.

In the usual test, a biopsy of the test site may be performed at the end of 6 to 8 weeks. The site may be surgically excised or a 5 mm. cutaneous punch may be used to obtain a core of skin and subcutaneous tissue. Sometimes the reaction papule in a positive Kveim test is only 2 or 3 mm. or less in diameter and it may be deeply placed, if the injection has been given too deep in the dermis. In such cases, palpation as well as inspection will be needed to detect the reactive test site.

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CRITERIA FOR A POSITIVE KVEIM TEST

The criteria used by various investigators as indicative of a positive Kveim reaction have not been uniform or rigid. Some have regarded the Kveim test as positive if a typical papule developed at the test site and persisted for several weeks or months. Danbolt[14] considers no reaction positive which does not show a distinct papule at the test site after a month and stipulates that this papule must persist distinctly for several additional months. If the papule is small and receding a month after injection, he would record the reaction as negative. Putkonen[6] considers no Kveim reaction to be positive unless the papule reaches a diameter of 5 mm. He places no time limit on the interval for reading the test. Nelson[10] has considered the Kveim test to be positive if a papule of any size occurs at the injection site and remains palpable for 60 days from the date of its appearance. Rogers and Haserick[19,21] have used the presence of a tuberculoid reaction resembling sarcoid in the excised test site, after 6 weeks, as the sole criterion of a positive Kveim test. Siltzbach and Ehrlich,[20] carrying the histopathologic approach to the extreme, obtain specimens for biopsy from all test sites 4 to 6 weeks after injection of the Kveim suspension, whether or not a reaction papule has developed. They would put no reliance upon the gross clinical reading but would have the histopathologic changes at the injection site constitute the only basis for classifying the Kveim reaction as positive or negative.

In the vast majority of cases, if the antigen used retains its reactivity and specificity, the development of a typical Kveim papule which persists at the test site for 6 to 8 weeks, would seem to suffice as an indication of a positive Kveim test. However, even with the best Kveim suspensions, papules may develop at the test sites which, to all intents and purposes, are clinically indistinguishable from the true Kveim papule but which, on excision, will reveal only a nonspecific granulomatous or banal inflammatory reaction without the characterictics of sarcoid. Considering the various factors involved in evaluating this test, it would seem best at the present time to regard the Kveim reaction as positive only if, first, a papule or area of induration can be seen or felt at the injection site after a period of 6 to 8 weeks, and second, if, upon excision of this reactive area, a tuberculoid response resembling sarcoid is found histologically. Test sites showing papules or areas of induration which yield nonspecific granulomatous reactions or banal inflammatory changes on histologic examination should be recorded as negative. If no reaction papule or definite induration is seen or felt at the site of injection after 6 to 8 weeks, the test should also be read as negative, without resort to biopsy.

Some investigators report that clinically nonreactive Kveim test sites at times may show typical tuberculoid granulomas on microscopic examination.[20,24] On the other hand, Rogers and Haserick,[19,21] as well as ourselves,[26] have found that when no papule or palpable infiltration is present at the Kveim test site within 6 to 8 weeks, such a site will reveal essentially normal skin or, at most, a mild nonspecific inflammatory reaction without granuloma formation, if it is excised at that point. With a potent and specific Kveim antigen, even a small degree of tuberculoid reaction may be expected to reflect its presence clinically as an area of induration or a papule at the test site. A Kveim antigen that behaves otherwise should be suspect.

Because biopsy of macroscopically nonreactive, i.e., "clinically negative", Kveim test sites, will in most instances yield negative results, it seems justifiable to interpret a Kveim test as negative when no clinically discernible reaction appears at the test site 6 to 8 weeks after the superficial injection of an antigen of known potency and specificity. It seems not too much to expect that an intracutaneous test which is to be worth its salt clinically should at least be seen or felt when positive. Other intracutaneous tests in clinical use today meet this basic requirement and the Kveim test should be no exception. Biopsy of the cutaneous reaction that isn't there clinically, that is, one that cannot be observed macroscopically, appears to be an unjustified extension of the Kveim testing technique, and one that may well serve as a source of confusion and error. That this is so, is suggested by the recent report of Sones and his co-workers[24] who found histologically "positive Kveim reactions" in 2 patients with tuberculosis. These reactions were obtained from Kveim test sites which showed no papule formation and which by ordinary skin-testing criteria would have been read as negative. It would seem better to run the risk of a few false-negative Kveim reactions, if such they may be called, than to overextend the Kveim testing technique to the degree that the incidence of false-positive reactions will be significantly increased.

HISTOPATHOLOGY OF THE KVEIM REACTION

Variations in the histologic appearance of the positive Kveim test have been studied by several investigators.[20-22] As Rogers and Haserick[21] have emphasized, with a potent and specific antigen of good quality, two main factors influence the resulting tissue reaction seen in the microscopic examination of a positive Kveim test. These are: (1) the individual's ability to react to the antigen; and (2) the duration of the test prior to excision.

The time interval between the injection of Kveim antigen and excision of the test site has an important influence on the histologic features of the positive test. If the Kveim reactive test site is excised before 4 weeks, the tuberculoid nature of the reaction may be too immature to recognize. If excision is delayed for 3 months, the histologic characteristics of the test are much more typical and often are indistinguishable from naturally occurring cutaneous sarcoidosis. However, to wait 3 months for the microscopic results of the test would seriously reduce its practical value as a diagnostic agent. Consequently, one should compromise between the above-mentioned extremes in selecting a suitable time interval between the injection of antigen and the microscopic examination of a Kveim reactive test site. Although some investigators favor an interval of 4 to 6 weeks, we prefer one of 6 to 8 weeks. The suggestion that the duration of the Kveim test, prior to excision of the reactive site, be set at 6 weeks[21] represents a middle ground which should satisfy most users of the test. This interval also has the virtue of eliminating from consideration the atypical or false-positive papules with long latent periods that have been reported by some investigators.[7,27]

At the end of 6 to 8 weeks, a positive Kveim reaction may vary from a few small tuberculoid aggregates high in the dermis to extensive infiltrations occupying the entire width of the dermis and extending into the subcutaneous tissue.

The epidermis is not involved by the process and the squamous epithelium remains histologically normal. In the less extensive positive Kveim reactions, foci of sarcoid tissue in the dermis are rounded in contour, averaging 2 mm. to 5 mm. in diameter. These lesions do not contain visible blood vessels, and lymphocytes are not present in large numbers. Epithelioid cells form the bulk of the structure and the focal collections of these cells are similar to those seen in naturally occurring sarcoidosis. In more extensive positive Kveim reactions, a small central area of pink-staining necrosis may be seen with the hematoxylin-eosin stain. An infiltrate of acute inflammatory cells may be found in the area of central necrosis and, surrounding this, there may be a zone of epithelioid cells and lymphocytes in which definite tuberculoid structures cannot be readily distinguished. Further in the periphery the reaction is less intense and epithelioid tubercles with minimal lymphocytic infiltration are present, resembling the tuberculoid structure of sarcoidosis. There is no involvement of the adjacent collagen. Giant cells, mostly of the Langhans type, may be seen in the foci of epithelioid tubercles and, occasionally, giant cells of other types with three or four centrally placed nuclei may be encountered. Although the cellular response in the area surrounding the central zone of epithelioid reaction is mainly lymphocytic, histiocytes and a few plasma cells may also be seen. Eosinophils and neutrophilic polymorphonuclear leukocytes ordinarily are not numerous.

As mentioned previously, the size and number of tuberculoid structures constituting a positive Kveim reaction will vary considerably with the patient's susceptibility to the stimulus and the potency of the antigenic suspension used. The highly reactive individual may respond violently at the point of maximum concentration of the antigen with complete necrosis of the tissue and an acute inflammatory reaction containing small central foci of suppuration. Although there is evidence that a positive Kveim response is associated in a high proportion of cases with activity of the disease,[6,13,14,19,20,29] the extent of the Kveim response probably cannot be used as an index to gauge the extent or severity of the sarcoidosis. Aside from a general association with the activity of the disease, the Kveim response does not seem to have any obvious relation to the type or degree of clinical involvement in patients with sarcoidosis.

The tuberculoid pattern of a positive Kveim reaction begins to emerge about 2 weeks after injection of the antigen. Prior to this, according to Rogers and Haserick,[21] there is an "active proliferative" phase, characterized by focal paravascular degeneration of collagen and a migration of histiocytes into the area. Then lymphocytes and pleomorphic cells appear in the areas of paravascular parenchymal degeneration and giant cells begin to form. With the emergence of the earliest tubercles the pleomorphic cells and lymphocytes begin to disappear. These changes take place within the first 2 weeks, but the process does not progress uniformly, and varying stages of its development may be seen at any one time in a single section. These authors feel that the early changes observed in a developing positive Kveim test are similar to the suspected early development of the naturally occurring lesions of sarcoidosis.

In the third week, the tuberculoid characteristics of the positive Kveim reaction are quite apparent and thereafter continue to become more conspicuous.[21]

As the proliferative phase wanes, the epithelioid tubercles become more and more "naked" and eventually tuberculoid structures having the appearance of the tubercles of sarcoidosis remain. The fully mature positive Kveim test after 6 to 8 weeks usually cannot be distinguished microscopically from the lesions of cutaneous sarcoidosis. This reaction pattern then persists relatively unaltered for weeks and months afterward.

A positive Kveim reaction occurs only when a reaction of similar morphology is taking place elsewhere in the host; but, unlike the lesions of the disease itself, the nodule of the positive Kveim test is almost invariably self-limited in its evolution. Although the test papule may persist for years if left undisturbed, progressive cutaneous lesions of sarcoid at the site of a positive Kveim test are rarely seen. Thus far, only two such occurrences have been reported.[21,30]

In view of the crude nature of the tissue suspension used in the Kveim test, it is to be expected that a certain number of patients with diseases other than sarcoidosis, and even some normal individuals, will develop reaction papules at the test site which are clinically similar to the typical Kveim papule. On histologic examination, however, these nonspecific inflammatory reactions reveal a microscopic picture quite different from the characteristic epithelioid reaction of a truly positive Kveim test. James and Thomson[22] have found these nonspecific reactions to be of three general types: (1) a banal inflammatory cell response, predominantly lymphocytic, usually found in the superficial dermis and greatest around hair follicles; (2) foreign-body granulomas with giant cells not of the Langhans type, an absence of epithelioid cells, and abundant polymorphonuclear leukocytes; and finally, (3) foci of epithelioid cells, giant cells, and lymphocytes, with the added feature of conspicuous necrosis which spreads beyond the cellular lesion to involve the adjacent collagen. The last type is the reaction which may be found in the few patients with active tuberculosis who produce a papular response when injected with Kveim antigen.

Apart from these types of reaction, the usual negative test shows essentially normal skin when excised or, at most, a few small aggregates of lymphocytes around the capillaries in the corium.

RESULTS OF THE KVEIM TEST IN SARCOIDOSIS

As has already been pointed out, the Kveim reaction has been studied by a number of investigators in various parts of the world during the past 15 years. In general, these studies have tended to confirm and extend Kveim's initial findings. These reports indicate that a positive Kveim reation may be expected in approximately 50 per cent to 90 per cent of patients with sarcoidosis, even when there is no evidence of cutaneous involvement.[1,6,10,13,14,16,20,21,23,29] For example, Putkonen[6] employed the Kveim test in 42 patients with proved sarcoidosis and noted positive results in 33. Danbolt,[14] reporting the results of several years' experience, obtained positive Kveim reactions in 41 of 46 patients with sarcoidosis. Siltzbach and Ehrlich[20] found the test positive in 50 of 58 patients with biopsy-confirmed sarcoidosis; and in the patients studied by Rogers and Haserick,[21] 49 with proved sarcoidosis yielded positive tests, while 8 were negative. Nelson and Schwimmer[23] reported positive Kveim reactions in 53

(74 per cent) of 72 patients with biopsy-confirmed sarcoidosis. On the other hand, Søndergaard[16] studied 29 patients with pulmonary sarcoidosis and found only 14 positive Kveim reactors in the group. A higher incidence of Kveim reactions in cases of pulmonary sarcoidosis, however, was reported by Nitter,[29] who observed a positive response in 61 (77 per cent) of 79 patients.

In the interpretation of the foregoing data on the sensitivity of the Kveim reaction, one should remember that these are over-all percentages, derived from patients with proved sarcoidosis but without regard to the state of activity of the disease. If the results of the Kveim test are studied solely in patients with progressive and obviously clinically active sarcoidosis, the incidence of positive reactions may be expected to be 80 per cent or more.[14,20,21,23]

There is now considerable evidence to suggest that Kveim reactivity bears a broad general relationship to the activity of the patient's sarcoidosis, and that regression of the disease process tends to lessen the response to the intracutaneous test.[6,10,13,14,20,21,23] Although a proportion of patients in ostensible remission will retain Kveim reactivity, a number will become Kveim-negative as their sarcoidosis regresses. Indeed, because of this, Nelson[13] has suggested that the test may be of occasional prognostic value in following the course of the patient's disease. He has observed a number of patients whose Kveim reactions were repeatedly positive during the clinically active stages of the disease, who lost their reactivity to Kveim antigen at the time when, or even slightly before, the disease process became clinically inactive.[23] It has also been found that some patients who originally give positive Kveim responses not only may become negative when the disease regresses clinically, but also may become Kveim-positive again later when there is recrudescence of the sarcoidosis.[23]

While it is true that the criteria by which the activity of sarcoidosis in a given patient may be judged are open to some question, we do not agree with Sones and his associates,[24] who feel that there are no dependable criteria for determining the activity of this disease. If, for example, no new lesions of the skin, mucous membranes, or bones are found for a period of one year or more, and if there has been no evidence of progression of ocular symptoms, hilar adenopathy, parenchymal involvement of the lungs, or superficial glandular enlargement during this time, one may feel reasonably secure in classifying the disease as inactive at that point. This is not to say that residual fibrosis of the lungs or chronic cor pulmonale, or other conditions may not persist or that new lesions of sarcoidosis may not develop after long intervals of quiescence. Should recrudescence of the disease occur, however, the careful observer should be able to detect that fact in the majority of cases and should be able to judge without great difficulty any relationship that may exist between Kveim responsiveness and activity of sarcoidosis. That this is so, is attested to by the data presented by Sones' group themselves,[24] who found that the percentage of positive Kveim reactions in patients whom they classified according to their own judgment as having "active" sarcoidosis was nearly double that observed in patients they believed to be in an "inactive" phase of the disease.

As has already been emphasized, the reaction to the Kveim test cannot be correlated with age, sex, color, tuberculin sensitivity, the levels of serum globulin, calcium or alkaline phosphatase, or the site and degree of organ involve-

ment. Some investigators[6,24] have suggested that patients with cutaneous sarcoidosis may react more often to Kveim material than those without skin lesions. However, Danbolt and Nilssen,[9] as well as others,[13,20] have not found that cutaneous involvement predisposes to a greater degree of reactivity to Kveim antigen. Should it be shown that patients with visceral sarcoidosis, without cutaneous lesions or peripheral lymph node involvement, react less frequently to Kveim antigen, it would seriously compromise the clinical value of the test, since it is in just those patients who have involvement of organs that are not readily accessible to biopsy, that the Kveim test should justify its usefulness. When there is a conveniently available lymph node or a cutaneous lesion of sarcoidosis, histologic proof of the disease can usually be provided without resorting to the Kveim test as a diagnostic measure. It is when such tissue is not available that the Kveim test should offer an easy alternative means for diagnosis and perhaps also serve as an index of the progress of the disease. More studies on the relationship of Kveim reactivity to the site and extent of sarcoidal tissue involvement are obviously needed. At present, however, the accumulated evidence would seem to indicate that Kveim reactivity is related much more closely to the activity of the disease than it is to the locale or degree of clinical involvement. Even the duration of the disease does not seem to have any consistent effect upon the outcome of the Kveim test.[20]

An additional factor that may influence the development and persistence of a positive Kveim reaction deserves mention. Rogers and Haserick[21] have shown that 5 mg. of hydrocortisone injected with Kveim antigen will prevent the formation of a tuberculoid reaction in patients with active sarcoidosis. Moreover, when a 6-week-old positive Kveim test site was injected with 5 mg. of hydrocortisone, considerable dissolution of the epithelioid tubercles was noted. It thus appears that hydrocortisone at the local tissue level may effectively block the stimulus responsible for the tuberculoid granuloma formation of the Kveim test, and may disperse the developing and developed granulomas. On the other hand, Rogers and Haserick[21] and James and Thomson[22] indicate that the effect of systemically administered corticosteroids on the Kveim reaction is irregular and difficult to evaluate. However, we[26] have observed that the administration of corticosteroids in sufficient dosage will consistently prevent the development of positive Kveim tests, and will cause an already positive Kveim test to disappear clinically. Discontinuance of the corticosteroid therapy in cases of active sarcoidosis will usually permit the redevelopment of another typical Kveim papule at the same test site. This waxing and waning of the Kveim test papule, with the cessation and readministration of adequate corticosteroid therapy, has been observed frequently by us and we believe it to be a fairly consistent phenomenon.

SPECIFICITY OF THE KVEIM REACTION

Most investigators who have studied the Kveim test extensively have found that the specificity of this reaction is high and that positive tests in normal individuals and in diseases other than sarcoidosis, are not common.[1,6,14,15,19-23] Until recently, the reported frequency of presumably false-positive Kveim reactions has not been great, ranging from 0 to 6.5 per cent. Those that were

observed merely seemed to reaffirm the truism that no biologic test, particularly one that employs an antigen as crude as the Kveim suspension, can be expected to be completely specific at all times.

Kveim,[1] in his original communication, mentioned that patients with diseases other than sarcoidosis did not respond to his test. Putkonen[6] observed two positive Kveim reactions among 65 individuals who did not have sarcoidosis. Danbolt[14] found positive Kveim reactions in 5 individuals in a group of 76 healthy adults and patients with diseases other than sarcoidosis. However, Danbolt considered any reaction positive which showed a distinct papule that persisted more than a month, and apparently he did not excise the test areas for microscopic verification. It is thus possible that some of these "false-positive" Kveim reactions may not have been histologically characteristic Kveim responses. Using two different Kveim antigens of known potency and specificity, Wade[15] found no positive Kveim reactions in 10 patients with lepromatous leprosy. Rogers and Haserick[19] observed two borderline Kveim reactions in 39 patients known not to have sarcoidosis. One of these occurred in a patient with erythema nodosum; the other in a case of possible erythema induratum. Siltzbach and Ehrlich[20] encountered two false-positive Kveim reactions in a control group of 54 patients. One of these false-positive tests occurred in a patient with idiopathic pulmonary fibrosis; the other in a 30-year-old woman with active and bacteriologically proved pulmonary tuberculosis. This patient was the only one of 16 individuals with tuberculosis who reacted to Kveim antigen. Rogers and Haserick,[21] in commenting on the results obtained by Siltzbach and Ehrlich, emphasize that the Kveim test is very rarely positive in tuberculosis. In their experience, none of 16 patients with active tuberculous infection developed a positive Kveim test. James and Thomson[22] encountered no false-positive Kveim reactions in 28 patients with tuberculosis and 19 patients with diseases other than sarcoidosis.

The largest single study on the specificity of the Kveim reaction is that by Nelson and Schwimmer.[23] These investigators studied the Kveim reaction in 234 persons who did not have sarcoidosis. They employed a single lot of Kveim antigen of established potency and specificity, prepared from sarcoid spleen tissue. The nonsarcoid patients comprising this study were classified into the following categories: (1) normal controls; (2) probably not sarcoid; (3) active tuberculosis, bacteriologically-proved; and (4) other diseases. The results of the Kveim tests in these 234 patients are summarized in Table I. These data show that none of the 18 normal individuals included in this series yielded positive Kveim reactions. Only one of the 35 patients in the "probably not sarcoid" group showed a positive Kveim reaction. (This category consisted of patients who exhibited a variety of clinical findings, one or more of which are sometimes associated with sarcoidosis. In these patients, subsequent observations often failed to establish a definite diagnosis, but as time elapsed it became evident that sarcoidosis was not a likelihood. In many instances, the Kveim test was performed merely because of a single suggestive laboratory finding without any real expectancy that the true diagnosis would be sarcoidosis). In this group, the only patient who gave a positive response to Kveim antigen had typical

TABLE I.* RESULTS OF THE KVEIM TEST IN 234 PATIENTS WHO DID NOT HAVE SARCOIDOSIS

DIAGNOSIS	NUMBER OF PATIENTS	POSITIVE KVEIM TESTS	
		NUMBER	PER CENT
Normal controls	18	0	0
Probably not sarcoid	35	1	3
Active tuberculosis, bacteriologically proved	99	1	1
Other diseases	82	0	0
Totals	234	2	0.9

*Adapted from Nelson and Schwimmer.[23]

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lesions of erythema nodosum at the time of testing and was later diagnosed as a case of probable beryllosis.

Of the 99 patients with active tuberculosis included in the report by Nelson and Schwimmer,[23] one had a positive Kveim reaction. Six additional patients with active tuberculosis developed small papules (1 to 3 mm. in diameter) at the sites of intracutaneous Kveim tests, but inasmuch as histologic examination of each of these test sites showed nonspecific inflammatory changes, the reactions were regarded as negative. Of the 82 patients with other diseases (that is, diseases other than sarcoidosis or tuberculosis, including a variety of generalized and cutaneous ailments of malignant, degenerative, infectious, and metabolic origin), none yielded positive Kveim reactions.

On the basis of the foregoing evidence, one may expect the incidence of false-positive Kveim reactions to be low in apparently healthy persons and in patients with diseases other than sarcoidosis. It may reach 6 per cent, but usually is considerably less. As Siltzbach and Ehrlich[20] have pointed out, this may be considered to be a satisfactorily low rate of false-positive reactions for a biologic test of this type.

Recently, however, Sones, Israel, and their co-workers,[24,25] have presented data purporting to show that the Kveim reaction is essentially without diagnostic specificity and that it is of no value in the differentiation of tuberculosis from sarcoidosis. These authors believe that the Kveim reaction cannot be relied upon as an aid in the diagnosis of sarcoidosis, and that the clinical use of the Kveim test is not justified. In their initial report, Sones' group[24] described the performance of 146 Kveim tests in 67 patients, using as antigens a suspension of sarcoid tissue and a filtrate derived from that source. Of these tests, 70 were made in 24 patients with histologic evidence of sarcoidosis, 38 in 19 patients with active tuberculosis, 15 in 6 individuals with suspected sarcoidosis, and 23 in 18 control subjects. Ninety-seven Kveim tests were performed with a 10 per cent suspension of sarcoid lymph node tissue prepared in the laboratories of the Henry Phipps Institute, University of Pennsylvania. This tissue was

obtained from a 30-year-old male Negro with systemic sarcoidosis involving lungs, peripheral lymph nodes, and parotid and lacrimal glands. With this material, Sones and his associates obtained positive Kveim responses in 11 (23 per cent) of 48 tests in the patients with sarcoidosis, in 8 (42 per cent) of 19 tests in the patients with tuberculosis, in 5 (62 per cent) of 8 tests in the sarcoid-suspects, and in 2 (9 per cent) of 22 tests in the control subjects. Two of the tests recorded as positive in patients with tuberculosis were obtained from test sites which showed no palpable nodule formation (i.e., sites which were clinically negative). Perhaps even more remarkable than these results is the finding of Sones and his co-workers that their Kveim antigen "filtered through coarse and ultra-fine, sintered glass filters" gave positive Kveim reactions in 6, or 27 per cent of the patients with sarcoidosis, in one, or 14 per cent of the sarcoid-suspects, and in one control subject. Heretofore, it has been believed that filtrates of Kveim antigens are inert.[6,14]

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In seeking an explanation for their inability to confirm the specificity of the Kveim reaction in the diagnosis of sarcoidosis, Sones and his group speculate on the possibility that the type of patient included in their series or the character of the sarcoidosis in their patients may have influenced their results. They also wonder whether the type and character of their control subjects may not account for the difference between their observations and those reported by others. Since reactivity to Kveim antigen is not known to be related to age, sex, color, type of clinical sarcoid involvement, alterations in blood chemical values, tuberculin sensitivity, or duration of the disease, the inability of Sones and his associates to confirm the specificity of the Kveim reaction cannot logically be explained on the basis of differences in the character of their clinical material. Although these investigators adopted the habit of obtaining biopsies from Kveim test sites even when no reaction papule could be observed clinically, the number of false-positive reactions found by them in this way apparently was likewise not sufficient to explain the discrepancy in their results. It seems much more likely that the failure of these investigators to corroborate the reliability and specificity of the Kveim test was due to deficiencies in their antigenic preparations or in their histologic interpretations of the tests, or both. The fact that they obtained positive Kveim reactions in 9 per cent to 42 per cent of patients known *not* to have sarcoidosis is prima facie evidence that the antigenic preparations used had lost their specificity and that they were not suitable for clinical testing. It hardly seems possible that minute differences in histologic preparation and in the interpretation of the tests could account for such impressive discrepancies. This may also be inferred from the fact that when these authors performed Kveim tests with antigens supplied them by other investigators, allegedly positive reactions were obtained in none of 5 patients with tuberculosis and in only one of 5 control subjects. Therefore, unless new evidence is presented to support the findings of Sones and his group, it would seem logical to recognize as probably valid the results of the majority of investigators who find that the specificity of the Kveim reaction is high and that positive tests are not common in patients with diseases other than sarcoidosis nor in normal individuals.

KVEIM RESPONSES WITH HETEROLOGOUS AGENTS

From the evidence already presented, it seems clear that the Kveim test has a high degree of specificity in the hands of most investigators. However, since the exact nature of the chemical complexes which are capable of inducing these tuberculoid tissue reactions in patients with sarcoidosis has not been determined, the question inevitably arises whether similar reactions can be produced in such patients by substances other than sarcoid tissue suspensions. Concerning this problem, it has been reported that reactions having some similarity to the Kveim response may sometimes be observed in patients with sarcoidosis after the intracutaneous injection of saline suspensions of leukemic human lymph nodes,[6] B. C. G.,[31-34] viable and heat-killed tubercle bacilli,[35-37] and even normal splenic tissue.[10] The fact that there may be several seemingly heterologous stimuli which are capable of producing Kviem-like responses in patients with sarcoidosis, however, in no way controverts or compromises the specificity of the Kveim reaction. Instead, such evidence merely suggests that Kveim-like responses may be due to one or more chemical complexes that may be present in a variety of substances. This should occasion no great surprise for, in the economy of nature, it would be more surprising if some of the chemical complexes contained in a tissue suspension as crude as the Kveim antigen were not shared by other agents, animate or inanimate. These, in turn, occasionally might be expected to induce tissue responses similar to those seen following the intracutaneous injection of Kveim antigen. But the finding that patients with sarcoidosis may react in an analogous fashion to certain heterologous substances provides no grounds for assailing the specificity of the Kveim reaction. One may as well deny the specificity of the reaction of pneumococcus Type 2 with its homologous antiserum because this organism shares an immunologically related capsular antigen with the B type of Friedländer's bacillus. By the same token, the fact that some patients with lymphogranuloma venereum may give positive skin test results with mumps antigen and old tuberculin, as well as Frei antigen, does not detract in any way from the specificity and clinical usefulness of the Frei test.

As a rule, the Kveim-like responses produced in patients with sarcoidosis by the heterologous substances mentioned above are irregular in occurrence and morphology. The reaction papules induced in sarcoid patients by the injection of suspensions of leukemic lymph nodes[6] were quite atypical in their evolution and required prolonged latent periods. Nelson's finding, that patients with sarcoidosis who exhibit a positive cutaneous reaction to the injection of Kveim antigen may also give a Kveim-like response to the intracutaneous administration of suspensions prepared from certain normal spleens,[10] has been confirmed in only one instance.[38] Other investigators have been unable to corroborate this observation.[14,20,21] In this connection, it should be emphasized that the production of Kveim-like responses in sarcoid patients by the injection of suspensions derived from apparently normal splenic pulp is an erratic occurrence. Of the 12 normal spleens studied by Nelson, 2 yielded suspensions which could produce these reactions and 10 were inert. This suggests that the production of this type of Kveim-like reaction in responsive sarcoid patients may depend on substances which are present in sufficient quantity in relatively few histologically normal spleens.

Again, efforts to elicit typical tuberculoid granulomatous responses in patients with sarcoidosis by means of injections of B. C. G. and heat-killed tubercle bacilli have also yielded variable results.[31-37] Apparently, the Kveim-like granulomatous reactions produced by these agents are not as consistent in occurrence and morphology as those induced with sarcoid tissue suspensions. Some investigators believe that the character of the local response to tubercle bacilli is related to the level of sensitivity to tuberculin.[33,39,40] Moreover, since acid-fast bacilli produce tuberculoid granulomatous responses almost as frequently in normal individuals as they do in patients with sarcoidosis, these reactions can have little significant diagnostic value.[33,37,39]

Other heterologous materials, organic and inorganic, have been used in efforts to induce responses comparable to the Kveim reaction in patients with sarcoidosis.[10,14] These, too, have failed and it now seems safe to say that most investigators who have studied the Kveim reaction in detail would probably agree that sarcoid tissue is a necessary ingredient in the antigen for the regular production of a morphologically typical Kveim response. As James and Thomson have pointed out,[22] sarcoid tissue is preferred as Kveim antigen because it produces positive and specific results in sarcoid patients more consistently than other substances.

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POSSIBLE MECHANISMS OF THE KVEIM REACTION

Ever since its inception, the Kveim reaction has excited the curiosity of investigators, not only because of its possibilities as a useful diagnostic test in sarcoidosis, but also because of its theoretical importance as a potential means for studying the pathogenesis of the disease. In his initial report, Kveim[1] postulated that the reaction described by him is an allergic cutaneous phenomenon, specific for sarcoidosis. However, the acceptance of this explanation encounters certain difficulties. If, for example, the Kveim reaction is allergic, in the ordinary sense of the term, it is not easy to explain why the cutaneous response characteristically does not appear until many days to several weeks after the administration of the antigen. Those who accept the Kveim reaction as allergic in nature presumably must regard this prolonged latent period as a manifestation of a delayed response in situ, caused by the reaction of antibodies in the sensitized host's tissues with an immobilized depot of particulate antigen.

Electrophoretic studies of the serum proteins in cases of active sarcoidosis often show an increase in gamma globulin, suggesting the possibility that antibody formation may occur in this disease in response to some as yet unidentified antigen or antigens. The inability to identify the antigen or antigens which might be responsible for such changes in the electrophoretic patterns of the blood serum in sarcoidosis, of course, does not negate the concept that some type of antigen-antibody phenomenon may be involved in this disease, and possibly in the Kveim reaction also. However, the fact that Kveim antigens can withstand boiling for 20 to 30 minutes without great loss of reactivity or denaturation suggests that the antigenic complexes responsible for the Kveim reaction probably are not simple proteins. Neither are they viable although, conceivably, they may be the products of viable agents.

In previous publications, Nelson[10,13] has suggested that the tuberculoid response to Kveim antigen in patients with sarcoidosis is determined not so much by specific immune processes, as by the nature of the substances introduced. He believes that the ability to react to Kveim antigen is peculiar to persons with active sarcoidosis, but that this reactivity, rather than necessarily being a specific antigen-antibody phenomenon, may intrinsically be but a general and characteristic reticulo-endothelial response on the part of persons with sarcoidosis to one or more chemical complexes. He suggests that the Kveim reaction in patients with active sarcoidosis may be a type of isomorphic tissue response to certain chemical substances contained in such things as Kveim antigen, and the lipid fractions of tubercle bacilli, among others.

Rogers and Haserick,[21] on the other hand, postulate that the Kveim reaction, in its simplest terms, may be regarded as the injection of a quantity of the responsible agent present in the tissues of one patient with sarcoidosis into the dermis of another patient. (Incidentally, although these authors do not stress the point, this responsible agent might be viable but, for reasons cited previously, it probably is not; it might be a product of the metabolism of a viable agent; or it might merely be a chemical complex peculiar to and contained in tissue showing the histologic changes which have come to be recognized as "sarcoid.") After injection of the Kveim material, the process that was taking place in the donor's tissue resumes in the recipient's skin, providing that the recipient, like the donor, has the ability to react to this agent. Since the ability to react to this agent is peculiar to persons with active sarcoidosis, this implies that the person with active disease must in some way be "sensitized" to the tuberculoid stimulating agent in the sarcoid tissue suspension. Moreover, this sensitivity, or altered reaction capacity, must be part of the active disease, since it tends to be lost when the disease enters a stage of remission, and is absent in persons who do not have sarcoidosis. While the existence of such a sensitizing antibody, as that postulated by Rogers and Haserick, is as yet entirely hypothetical, they feel that its presence would permit a relatively simple explanation for a phenomenon that is otherwise difficult to explain. Since the epithelioid reaction in sarcoidosis is in itself nonspecific and merely a host response to one of a number of possible stimuli, these investigators envision the epithelioid tubercles found in the positive Kveim test as possibly being the result of a union of antigen with antibody. In other words, they postulate that the formation of a positive Kveim reaction is essentially a tissue response resulting from the union of antigen and antibody in situ. As these authors point out, proof of this concept will rest upon the isolation of the active antigenic fraction from sarcoidal tissue and the demonstration that the end result (sarcoidlike granuloma) arises from the union of antigen and antibody.

In support of their hypothesis, Rogers and Haserick[21] cite experiments to show that if sarcoidal gamma globulin is injected into the skin of a healthy person only a mild irritation ensues. If Kveim antigen is injected into the skin of a healthy person, there is no appreciable reaction after a few days. If, however, sarcoidal gamma globulin and Kveim antigen are mixed and injected into the skin of a healthy person, considerable erythema results at the site of injection,

followed by the development of an indolent papule, which at 4 weeks will show focal areas of epithelioid cells surrounded by lymphocytes. These are interesting findings which deserve further investigation. In themselves, however, they are merely suggestive, for it must still be shown that this response is specific for the mixture of Kveim antigen and sarcoidal gamma globulin. It would be important to know whether gamma globulin fractions from other hyperglobulinemic conditions and from normal sera share this potentiating effect on Kveim antigen.

From this summary, it is obvious that there is no generally accepted hypothesis which might explain the nature of the characteristically delayed granulomatous response seen in the positive Kveim reaction. The first step needed in the elucidation of this phenomenon would seem to be the isolation of the antigenic fraction or fractions from sarcoidal tissue. Presumably, this will rest not on the recovery of a viable agent, but will depend on the chemical identification of the substances contained in sarcoid tissue which are responsible for the characteristic Kveim reaction. After the chemical identity of the responsible antigenic fractions has been established, there will still remain the problem of determining why the ability to react to this agent is peculiar to the person with active sarcoidosis. If this, in fact, is the result of an antigen-antibody reaction then, as Rogers and Haserick have noted,[21] the basic mechanism of both the Kveim reaction and naturally occurring sarcoidosis may at last be uncovered.

The Kveim test, which has been found to be a reliable and useful confirmatory diagnostic aid in patients with sarcoidosis, is one of the few significant developments in the study of this disease in recent years. The test is generally specific for sarcoidosis and may be of considerable diagnostic use, especially when tissues from involved organs are not readily accessible for biopsy. Although the Kveim test in its present form has obvious limitations as a means of diagnosis, it is hoped that further study of its evolution and behavior may shed some much needed light on the question of the pathogenesis of the naturally occurring disease.

Some investigators are convinced that the papule at the site of a positive Kveim test is fundamentally a lesion of sarcoidosis, that is, that the reaction to sarcoidal tissue suspension in a patient with active sarcoidosis is the same host response that occurs elsewhere in the patient as a part of his disease. The unknown character of the chemical complexes contained in the antigen, however, remains a severe handicap to a real understanding of the nature of this altered tissue reactivity on the part of the host. Although the concept of sarcoidosis as a process which involves antigen-antibody mechanisms remains unproved, observations on the course and development of the positive Kveim test may, in the future, provide additional information on this point. Most of the features of sarcoidosis are consistent with those of a chronic granulomatous process having a special predilection for the tissues of the reticulo-endothelial system. The question of the etiology of sarcoidosis is still far from being solved, and in the present state of knowledge, it does not appear likely that further careful bacteriologic and viral studies will contribute much to the solution of this problem. Additional investigations of the mechanisms of the Kveim test may be more useful in revealing the underlying pathogenesis of sarcoidosis.

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SOME CONSIDERATIONS PERTAINING TO THE PROPER USE OF SUPPLEMENTARY VITAMINS

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THIS discussion is not intended to review all of the conflicting opinions as to the use of vitamins; others[1,2] have assembled extensive bibliographies on this subject. Instead, this presentation attempts to state the author's opinion as to the major considerations bearing on the use of vitamins.

An understanding and appreciation of the following basic considerations underlie the proper medical use of vitamin preparations: (1) Vitamins are essential organic nutrients, the normal source of which is food. (2) An appropriately varied diet, such as is usually consumed in the United States, supplies a sufficient quantity of those nutrients required by man to meet his requirements except under unusual circumstances. (3) There is no more justification for indiscriminate prescription of vitamin preparations than for any other medicament. (4) Vitamins are therapeutically useful in rather specific situations in which there is a readily recognizable deficiency state and, despite widely made uncritically considered claims, the nonspecific, general toniclike usefulness so often attributed to vitamins is merely a placebo effect.[3] (5) Conditioning factors may increase the needed daily intake of vitamins and, hence, in certain situations justify a use of protective supplementation. (6) In a few instances gross overdosage with certain vitamins may be harmful[4-9] and even fatal. (7) It is poor medical practice to allow even a harmless form of medication to substitute for the establishment of a definite diagnosis or the institution of a proper therapeutic regimen. (8) The cost to the patient of vitamin preparations is not inconsiderable.

Therapeutically it is useful to categorize the use of vitamins into those classes suggested by Youmans.[10]

1. Curative treatment is the clearly specific administration of factors to correct an evident deficiency state. Such treatment results in recognizable rapid clinical betterment in the patient. But in contrast to the eradication of an infection with an antibiotic, the cure of the deficiency resulting from administered vitamin preparations does not remove the cause of the disease. The cause resides in economic, educational, or emotional factors which result in severe dietary restriction, or in some medically conditioning factor. In no instance

is permanent cure effected by temporary supplementation without simultaneous correction of the basic cause of the deficiency.

A conditioning factor is any process which increases the requirement of a nutrient above the usual level. Such an increased need may result from excessive loss (e.g., chronic blood loss conditions a deficiency of iron), failure to absorb (thus, in steatorrheas a decreased efficiency of absorption of fat-soluble factors exists and may give rise to deficiencies of vitamins K, D, A, E, or carotene), an increased demand created by a disease (e.g., hyperthyroidism increases to a varying extent the caloric and thiamine requirements), or by a physiologic state (thus, the rapid growth of children aged 9 to 15 years or the great drain of lactation may bring about appreciable increases in dietary requirement above the level of usual maintenance for the group).

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2. Protective treatment is the prevention of the development of deficiency states in individuals who are especially exposed to the possibility of a deficiency. This possibility is often the result of some conditioning factor, for example, mild chronic excessive loss of blood may lead to iron lack, or obstruction of the common bile duct leads to defective fat absorption and, thereby, allows the development of a deficiency of vitamin K.

Another type of protective therapy is that employed as replacement of a nutrient in which an abnormally (but perhaps purposely) restricted diet is deficient. Such restricted diets may result from many causes, such as a grossly distorted dietary habit in some psychiatric cases or a prolonged imposed therapeutic regimen. Instances of need for the latter are increasingly rare in modern diet therapy, for the therapeutic diet is now widely regarded as but a modification of the normal dietary or a control of the quantity of the dietary in such manner as to fill a particular need, and the modification must be so planned as to preserve the nutrient composition of the normal diet.[11] In keeping with this concept, most modern, properly designed therapeutic diets provide adequate amounts of vitamins in the foods, and there is no need to give supplements to the diet.

3. Preventive supplementation is that designed to offer widespread general prevention in the population as a whole and includes the addition of specific nutrients to foods, along with such measures as education as to food values, improving the availability and variety of foods, and other general nutritional measures. The Council on Foods and Nutrition of the American Medical Association and the Food and Nutrition Board of the National Research Council have jointly adopted[12] a carefully considered and well-stated general policy in regard to the addition of specific nutrients to foods. This states:

> (1) With carefully defined limitations, the principle of the addition of specific nutrients to certain staple foods is endorsed for the purpose of maintaining good nutrition as well as for correcting deficiencies in the diets of the general population or of significant segments of the population. The requirements for endorsement of the addition of a particular nutrient to a particular food include (a) clear indications of probable advantage from increased intake of the nutrient, (b) assurance that the food item concerned would be an effective vehicle of distribution for the nutrient to

TABLE I. FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL RECOMMENDED DAILY DIETARY ALLOWANCES,* REVISED 1953

DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY PERSONS IN THE U.S.A.

(Allowances are considered to apply to persons normally vigorous and living in temperate climate)

	AGE YEARS	WEIGHT KG. (LB.)	HEIGHT CM. (IN.)	CALORIES	PROTEIN GM.	CALCIUM GM.	IRON MG.	VITAMIN A I.U.	THIAMINE MG.	RIBOFLAVIN MG.	NIACIN MG.	ASCORBIC ACID MG.	VITAMIN D I.U.
Men	25	65 (143)	170 (67)	3200†	65	0.8	12	5000	1.6	1.6	16	75	
	45	65 (143)	170 (67)	2900	65	0.8	12	5000	1.5	1.6	15	75	
	65	65 (143)	170 (67)	2600	65	0.8	12	5000	1.3	1.6	13	75	
Women	25	55 (121)	157 (62)	2300†	55	0.8	12	5000	1.2	1.4	12	70	
	45	55 (121)	157 (62)	2100	55	0.8	12	5000	1.1	1.4	11	70	
	65	55 (121)	157 (62)	1800	55	0.8	12	5000	1.0	1.4	10	70	
	Pregnant (3rd* trimester)			Add 400	80	1.5	15	6000	1.5	2.0	15	100	400
	Lactating (850 ml. daily)			Add 1000	100	2.0	15	8000	1.5	2.5	15	150	400
Infants‡	0-1/12§												
	1/12-3/12	6 (13)	60 (24)	kg. x 120	kg. x 3.5‡	0.6	6	1500	0.3	0.4	3	30	400
	4/12-9/12	9 (20)	70 (28)	kg. x 110	kg. x 3.5‡	0.8	6	1500	0.4	0.7	4	30	400
	10/12-1	10 (22)	75 (30)	kg. x 100	kg. x 3.5‡	1.0	6	1500	0.5	0.9	5	30	400
Children	1–3	12 (27)	87 (34)	1200	40	1.0	7	2000	0.6	1.0	6	35	400
	4–6	18 (40)	109 (43)	1600	50	1.0	8	2500	0.8	1.2	8	50	400
	7–9	27 (59)	129 (51)	2000	60	1.0	10	3500	1.0	1.5	10	60	400
Boys	10–12	35 (78)	144 (57)	2500	70	1.2	12	4500	1.3	1.8	13	75	400
	13–15	49 (108)	163 (64)	3200	85	1.4	15	5000	1.6	2.1	16	90	400
	16–20	63 (139)	175 (69)	3800	100	1.4	15	5000	1.9	2.5	19	100	400
Girls	10–12	36 (79)	144 (57)	2300	70	1.2	12	4500	1.2	1.8	12	75	400
	13–15	49 (108)	160 (63)	2500	80	1.3	15	5000	1.3	2.0	13	80	400
	16–20	54 (120)	162 (64)	2400	75	1.3	15	5000	1.2	1.9	12	80	400

*In planning practical dietaries, the recommended allowances can be attained with a variety of common foods which will also provide other nutrient requirements less well known; the allowance levels are considered to cover individual variations among normal persons as they live in the United States subjected to ordinary environmental stresses.

†These calorie recommendations apply to the degree of activity for the reference man and woman. For the urban "white-collar" worker they are probably excessive. In any case, the calorie allowance must be adjusted to the actual needs of the individual as required to achieve and maintain his desirable weight.

‡The recommendations for infants pertain to nutrients derived primarily from cow's milk. If the milk from which the protein is derived is human milk or has been treated to render it more digestible, the allowance may be in the range of 2 to 3 Gm. per Kg. There should be no question that human milk is a desirable source of nutrients for infants even though it may not provide the levels recommended for certain nutrients.

§During the first month of life, desirable allowances for many nutrients are dependent upon maturation of excretory and endocrine functions. Therefore no specific recommendations are given.

be added, and (c) evidence that such addition would not be prejudicial to the achievement of a diet good in other respects. These requirements have been met in the specific cases indicated in paragraph (6).

(2) The desirability of meeting the nutritional needs of the people by the use of natural foods as far as practicable is emphasized, and to that end education in the proper choice and preparation of foods and the betterment of food production, processing, storage, and distribution so as to provide more fully the essential nutrients native thereto are to be encouraged.

(3) In order to avoid undue artificiality of food supply, foods chosen as vehicles for the distribution of additional nutrients should be, whenever practicable, those foods which have suffered loss in refining or other processing, and the nutrients added to such foods should preferably be the kinds and quantities native to the class of foods involved.

(4) The addition of other than natural levels of nutrients to foods which are suitable vehicles of distribution may be favored when properly qualified judgment indicates that the addition will be advantageous to the public health and when other methods for effecting the desired purpose appear to be less feasible.

(5) Whenever technologic and economic developments lead to extensive reduction in the consumption of a staple food, with a consequent nutritionally significant reduction in the intake of an essential nutrient or nutrients, consideration by qualified bodies should be given to the desirability of restoring such nutrient or nutrients to the dietary.

(6) The endorsement of the following is reaffirmed: the enrichment of flour, bread, degerminated corn meal, and corn grits; the nutritive improvement of whole grain corn meal and of white rice; the retention or restoration of thiamine, niacin, and iron in processed food cereals; and the addition of vitamin D to milk, of vitamin A to table fats, and of iodine to table salt.

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This policy is clearly not one designed to disperse therapeutic levels of vitamins in the food supply. Instead, it is aimed at improving the food supply through assuring that certain foods contain either a restored or a preventive quantity of certain nutrients. It is only in the instance of the addition of vitamin D to milk and of iodine to table salt that the quantities of nutrient added are designed to supply in a daily portion of the food the full amount of the needed nutrient. The level of the vitamin D addition to milk is set to supply 400 I.U. per quart of fluid milk or, in the case of evaporated milk, of reconstituted product. This level is chosen so that the intake of a quart of milk daily will meet the standard of intake of vitamin D which is believed desirable in most cases.

Perhaps the most widely used standard of desirable intake of nutrients is the Recommended Dietary Allowances[13] of the Food and Nutrition Board (Table I). These allowances are designed as standards for use in planning practical, adequate dietaries for normal individuals in the United States. They are *not* intended as minimal requirements nor as standards for feeding under conditions of special needs (except as specified). They, therefore, give a useful measuring scale for determining the suitability of the content of a proposed diet, therapeutic or maintenance, for long-term use. Comparison of the vitamin content of a diet with this yardstick aids in ascertaining any possible justified need for supplementary vitamin administration for preventive care or protective therapy in instances without increased metabolic demands due to disease states.

The magnitude of any increased needs of vitamins due to disease is a point on which there is much opinion but little objective information. Accordingly, the tentative Recommended Daily Dietary Allowances for Public Health Service

Hospitals[14] (Table II) is a reasonable guide to a generous but attainable dietary intake judged to meet the average need of the total hospital population which consists primarily of men, a high proportion of whom are ambulatory and who are accustomed to hard physical work.

TABLE II. RECOMMENDED DAILY DIETARY ALLOWANCES FOR PUBLIC HEALTH SERVICE HOSPITALS (TENTATIVE)

	CALORIES	PROTEIN	CALCIUM	IRON	VITAMIN A	THIAMIN	RIBOFLAVIN	NIACIN	ASCORBIC ACID	VITAMIN D
		Gm.	Gm.	mg.	I.U.	mg.	mg.	mg.	mg.	I.U.
Nutrition Standards Public Health Service Hospitals										
General and Neuropsychiatric	3,000	100	1.5	12	5,000	1.8	2.0	18	75	—
Tuberculosis and Leprosy	3,600	125	2.0	15	5,000	2.0	2.0	20	100	400
Clinical Center	2,700	95	1.5	12	5,000	1.6	1.9	16	75	—

The figures above represent food as served to the patient (not actual intake). They do not include any allowance for wastage in food preparation.

Additional Recommendations: 1. All salt should be iodized. 2. All bread, flour, and corn meal should be "Enriched." 3. All milk for patients with tuberculosis and leprosy should be fortified with vitamin D. 4. About 20 per cent of calories should come from fat in regular diets; about 33 per cent from fat in high calorie diets.

No acceptable evidence is known to me that an intake of vitamins greater than that provided by the Recommended Dietary Allowances or the Recommended Daily Dietary Allowances for Public Health Hospitals (Tentative) is beneficial to the patient. These levels can be attained by properly planned menus without administering supplementary vitamins. If, however, circumstances prevent attaining them, it may be reasonable to supply the patient with supplementary vitamins in amounts sufficient to assure such an intake. If a patient enters an illness in a well-nourished state, this precaution would appear necessary only if the intake were expected to remain at a low level for a period of several weeks.

It is not always appreciated that depletion of moderately well-nourished adults requires a variable period of from weeks to years. Thus, for biochemical depletion of vitamin C in adults[15] it requires 4 to 16 weeks of C-free or grossly deficient diet, and for the first appearance of minor clinical evidences of scurvy 17 to 21 weeks. Interference with normal wound healing is detectable after 5 to 8 months. Depletion of riboflavin to a point of developing ariboflavinosis occurs in 27 to 36 weeks[16]; following the cessation of therapy with folic acid, patients with sprue relapse in some 3 to 6 months.[17] Similar periods of depletion seem required for niacin and thiamine. Withholding of treatment with liver extract or vitamin B_{12} from patients with pernicious anemia was followed by continued remission for periods ranging from 5 months to 13 years.[18] It seems logical, therefore, to regard a period of a few days of restricted or low intake of

water-soluble vitamins as without any particular significance and to judge that the routine administration of supplementary vitamins in acute illness of but a few days' duration serves no beneficial purpose.

The body's capacity to retain the fat-soluble vitamins seems to exceed that of the water-soluble ones. Thus, the development of the earliest evidence of avitaminosis A within a group of volunteers required 10 to 20 months.[19] Again, short periods of deprivation can certainly be tolerated without harm.

Vitamin supplementation as protective therapy is justified whenever there is a prolonged (for more than a few weeks) intake clearly below the Recommended Dietary Allowances. The nature of the Recommended Dietary Allowances is such as to make it impossible to set a single, fractional portion of the recommended intake for all vitamins at which supplementation becomes desirable. Conversely, it is reasonable to regard a multiple of one or two times the recommended allowance of a vitamin as an appropriate protective supplement in most instances.

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Effective therapeutic doses of vitamins vary over a wide range. Remissions of classical deficiency states will readily follow the ingestion of 5 to 10 times the quantity regarded as a good dietary intake, i.e., 5 to 10 times the Recommended Dietary Allowance of the vitamin. Daily ingestion of this quantity, likewise, will permit the reaccumulation of appreciable stores of the deficient factor and, in the instance of the water-soluble vitamins, does not result in as great initial urinary wastage as do larger intakes. Urinary wastage is less with oral dosing and, where feasible, the oral route is preferred to the parenteral (except, of course, in the instance of vitamin B_{12}). There is no advantage to continuation of the therapeutic dosage level of vitamin supplements for longer than 10 days or 2 weeks. Upon recognition of a deficiency state, the physician should make a vigorous effort to correct the dietary habit of the patient. During the period of dietary re-education or correction it may be well to continue supplementation for longer than the initial 2-week interval; if so, the continuing dosage should be at the lower "protective therapy" level. After successful correction of the food habits and the establishment of a good dietary intake of the vitamins from food, there is no need for further supplementation.

Useful chemical methods[11,20,21] are available to assist in ascertaining when the patient's stores of several vitamins have been replenished and, when further supplementation is, therefore, unnecessary. This state pertains whenever the fasting plasma ascorbic acid level exceeds 0.6 to 0.8 mg. per 100 ml. or when the serum concentration of vitamin A rises to above 120 I.U. per 100 ml. Somewhat less convenient urinary studies must be relied on for appraisal of nutriture of thiamine, riboflavin, or niacin. These tests may be made on either fasting timed specimens or on timed (6-hour) specimens collected after oral ingestion of a standard dose of the vitamin. A convenient load test is one in which 5, 5, and 50 mg., respectively, of riboflavin, thiamine hydrochloride, and nicotinamide are administered orally and the urine collected for a period of 4 hours. Riboflavin, thiamine, and *N'*-methylnicotinamide are then determined. The excretion of amounts in excess of 1.0 mg., 0.2 mg., 7 to 8 mg. may be regarded as evidence of good tissue stores. Similarly, a 6-hour timed fasting urinary

excretion of riboflavin, thiamine, and *N'*-methylnicotinamide of 0.1 mg., 0.05 mg., and 1.6 mg. or more, respectively, supports the judgment of ample body stores.

It is my opinion that the usefulness of these reliable objective measures has not been appropriately recognized. They can give clear evidence of the attainment of good stores of these vitamins and the uselessness of further supplementary dosage. They are also useful in appraising the faithfulness of the patient in pursuing therapeutic instructions as to supplements, as well as his adherence to corrective dietaries. Failure widely to explore these tests is probably due to the many differences of opinion arising over the question of their reliability in diagnosing deficiency states, especially of "borderline degree."

Equally convenient procedures are not yet available for other vitamins, except tocopherols. Furthermore, recent studies indicate that procedures employing blood may become useful for at least some of those appraisals now limited to urine. For example, Bessey[22] finds that the riboflavin content of erythrocytes may be a sensitive method for assessing nutriture in respect to this vitamin.

Avoidance of excessive and unnecessary supplementation is to be desired on the same grounds as any other type of unwarranted therapy—it is an unnecessary expense to the patient; it promotes uncritical appraisal of the patient by the physician; and it may be potentially harmful. In this latter regard we need but remind the reader of the occurrences and consequences of hypervitaminosis A[4,5,6] and D.[7,8,9] Evidence[23] in the human of hypervitaminosis from any water-soluble vitamin is exceedingly meager and unconvincing, but the uselessness of excesses is ample reason to avoid excessive administration.

Several nutrients are recognized essentials for nonhuman species, but the dietary dependence of man for them is not established. The question arises as to whether these factors should be given to patients. A rational attitude would seem to dictate that such factors not be so given unless the physician clearly recognizes the nature of the factor administered and is deliberately testing its efficacy in the condition at hand. Vitamins for which unquestioned deficiencies occur in man are: Vitamins A, D, K, thiamine, riboflavin, niacin, ascorbic acid, pteroylglutamates (folic acid), vitamin B_{12}, and pyridoxine. Studies with antivitamins[24] demonstrate that pantothenic acid is essential in metabolism, but do not as yet establish a dietary dependence for it by the human. Metabolic effects of tocopherols in man[25] and evidence interpretable as tocopherol deficiency have recently been presented. The spectrum of vitamins which promises to find a legitimate role in therapy is obviously increasing. Acceptance of claims for such roles in human nutrition must be critically appraised, for otherwise one could readily draw the fallacious conclusion that one or another vitamin or combinations thereof will cure practically all the diseases to which man is susceptible, but for which physicians do not have effective specific curative agents—diseases and conditions ranging from alcoholism to sterility. Insistence upon consistent clear-cut clinical responses and evidences of metabolic effects before accepting claims concerning vitamins for human use should serve as proper guides in deciding on the potential usefulness of a particular factor.[26] The

physician must bear in mind, however, that the existence of acceptable evidence as to the role of a vitamin in metabolism of man does not constitute evidence for its therapeutic usefulness in any disease. This must be separately appraised.

Critical examination of the multitude of conditions reportedly influenced by each vitamin leads one to the inevitable conclusions that most authors have failed completely to recognize the therapeutic effectiveness of placebos[27] and suggestion, and that the relatively innocuous vitamin pill has been accorded an unreasonable and unsubstantiated breadth of usefulness. Indeed, the alleged effectiveness of one vitamin after another on the same stubborn but undulating condition speaks for a repeated observation of a placebo effect and for the widespread habit of drawing conclusions from uncontrolled observations.

The effectiveness and usefulness of vitamins as supplements is limited to the prevention and treatment of deficiency states—a usefulness which places them among the most valuable of therapeutic agents—and as placebos.[28,29] The greatest contribution of supplementary vitamins to the positive health of the population is to be made through appropriate, considered employment of them in preventive, protective, and curative therapy. On these grounds they often have an important place in the management of patients with chronic diseases. However, examination of the justification for vitamin therapy in each patient will materially offset the spurious appeal of multicolored products whose qualitative and quantitative composition has long since escaped the prescriber.

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Book Reviews

WHITLA'S DICTIONARY OF MEDICAL TREATMENT. R. S. Allison, M.D., and T. H. Crozier, M.D. Ninth edition. Baillier, Tindall and Cox, London, England. Pp. 854, indexed. Price $10.50.

The authors of this book attempt to cover all of "medical therapeutics" in 800-odd pages. The subjects covered range from acne to ankylostomiasis, child guidance to coccydynia, writer's cramp to water requirements. The results are (with some exceptions) as superficial and unsatisfactory as one might anticipate. There may have been a need for such a book in 1891, the year of its first edition; it is depressing to imagine a demand for it today.

Louis Lasagna, M.D.

PROBLEMS OF AGING. Edited by Robert L. Craig, M.D. Pp. 340, illustrated. New York, 1956, Charles C. Morchand Co. Price $3.50.

This paper-bound volume contains a collection of lectures presented at the Graduate Fortnight of the New York Academy of Medicine in October, 1955, and published in 1956 in the Bulletin of the New York Academy of Medicine. It is presented in this form as a reference for those interested in the problems of aging. Only a few of the lectures deal with the biologic process of aging, the majority deal with diseases in older people. Indeed, the collection might have been called more accurately "Medical Problems of the Aged."

In a monograph on aging, one might logically expect to find out what aging is, and how it may be distinguished from disease processes. The answers given by different authors are somewhat contradictory. Albert Lansing, in "What is Aging," states that aging invariably results in death of the organism. Such a statement certainly could not be accepted by most pathologists who are usually able to identify a disease process as the cause of death. The same author goes on to say, "We agree that there must be at least some structural and functional changes in aging but in essence we have failed to characterize them."

In a later article on the experimental prolongation of the life span, Clive McCay reports on experiments carried out with white rats. He concludes, "From our research of more than a quarter of a century we are convinced that when one lengthens the life span of an animal such as a white rat, he does so by retarding the onset of certain chronic terminal diseases." This statement agrees with clinical medical opinion.

In his article on some physiologic aspects of aging in man, Shock faces the issue of aging squarely. He recognizes that "age changes as identified today may represent states of early pathology." His studies are done in people of different ages in the absence of diagnosible disease states.

Dickinson Richards in his article on the aging lung points out that elastic tissue is definitely reduced in the lungs of old people, but it is not clear as to whether he considers this change a result of normal aging or a pathologic process.

The question as to what aging is, therefore, is never clearly answered, and the result is that one finds it difficult to formulate ideas to test by experimentation in this field. According to Lansing, it is the lack of clues that might direct research into specific avenues that accounts for the small number of workers in the field of aging.

The article on psychologic aspects of aging by Ross McFarland is an excellent report on the differences in sensory and mental performance in different age groups. It is pointed out that judgment, reasoning, and other complex psychologic functions are more resistent to deterioration

with age than more simple psychologic functions. This study is oriented toward the industrial efficiency of older workers and is of value to anyone interested in performance of older individuals in industry.

The remainder of the articles are clinical in nature, dealing with disease in older people. Many authors emphasize the impairment of homeostatic capacities of the older person under conditions of stress such as gastrointestinal hemorrhage, excessive fluid administration, excessive work loads, or emotional pressures.

Most of the clinical problems of older people are covered, but some, such as cancer, cerebrovascular accident, prostatism, and renal disease are not mentioned and some of those discussed are so specialized as to serve little purpose as a "review in concise form" which is the stated purpose of the monograph. Indeed the incompleteness of "Problems of Aging" seems to be its principal weakness, and it is difficult to justify its publication as a collection, when the original articles are already available in the literature.

This is not to say that it does not contain excellent articles of clinical value. Among these, the article on osteoarthritis by Joseph Bunim is especially comprehensive, clear, and concise. John S. LaDue's article on evaluation and preparation of the patient with degenerative cardiovascular disease for major surgery is important for anyone dealing with older patients. Robert H. Kennedy in "Management of Injuries in the Aged" emphasizes the treatment of the patient in the light of his past interests, attainments, and possibilities. A comparison of two articles, the first by Condict W. Cutler, Jr. on the management of surgical emergencies in the aged, the second by Frank Glenn on surgery in the aged reveals a remarkable difference in mortality rates with the same operation. The first article is a report on indigent inmates of city institutions, many of whom were already in the hospital for chronic diseases other than the surgical emergency. The mortality rate was therefore quite high. The second article describes results in patients presumably on acute surgical wards, many of whom entered the hospital for elective surgery, some of whom may have been private patients. The mortality rates and percentage of associated diseases is smaller than in the first report. The point is that both groups were chronologically aged, but the results of surgery were dependent less on chronologic than on physiologic age and associated diseases.

Douglas Carroll, M.D.

HOSPITAL PATIENT SURVEY. By Howard A. Rusk, M.D., John E. Silson, M.D., M.P.H., Joseph Novey, M.S.W., and Michael M. Dacso, M.D. Published by Hospital Patient Survey, 1956. Pp. 146, with 72 charts. Welfare Island, New York, Goldwater Memorial Hospital.

Every hospital dealing with an indigent population contains a group of patients who no longer need active medical care but who, for various reasons, cannot be discharged to home or to a less specialized institution. This survey is an attempt to assess the number and characteristics of this group of patients in the municipal hospitals of New York City. Tuberculous and mental patients were excluded from the study. Twenty per cent of the total (10,000) hospital population selected by approved statistical methods was investigated by a field team. All types of medical, economic, and sociologic data with estimates of prognosis, future employment status, rehabilitation needs, and potential are reported in the 72 charts and 146 pages of text.

Some of the interesting findings were that 34 per cent of the total hospital population had hypertensive, arteriosclerotic, or other degenerative heart diseases, 10 per cent were hemiplegic, 11 per cent had fractures, 10 per cent had malignant neoplasms, whereas only ½ of 1 per cent had acute appendicitis, and a total of 5 per cent had infective or parasitic diseases. These figures demonstrate the preponderance of patients with chronic diseases accumulating in municipal institutions.

The data describing the existing features of the patients are excellent. The tables, depending on the opinions of the field team, however, are more difficult to appraise since the criteria on which its decisions were made are not always included. The table entitled "Estimated Future Length of Stay for Medical Reasons by Potential Disposition (Including Rehabilitation)" seems to be especially tenuous. Yet it is on such opinions that planning for new facilities must be based. In general, the decisions reached by the team appear to be carefully weighed.

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Almost 20 per cent of the sampled patients were found to require no further hospital care but, for lack of appropriate facilities and for various social and economic reasons, could not be discharged from the hospital. The majority of these patients had cardiovascular, neurologic, or musculoskeletal disabilities. It was estimated that 82 per cent could be cared for in a nursing home or specialized institution, and the rest could be cared for at home with medical supervision.

The solution suggested is early rehabilitation of patients who may benefit and the establishment of institutions of the nursing home type.

This survey reveals little that was not known in a general way. It quantitates the magnitude of the problem and gives a basis for future planning. Its main value outside of New York City is to stimulate and to indicate an approach to this problem in other parts of the country.

Douglas Carroll, M.D.

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PRACTICAL DERMATOLOGY. By Samuel M. Peck, B.S., M.D., with Laurence L. Palitz, M.D., Ph.D. Pp. 380, with 122 figures; indexed. New York, 1956, Landsberger Medical Books, Inc. (Distributed solely by The Blakiston Division of the McGraw-Hill Book Co.) Price $7.00.

This is the sixth in a series of small reference books for the general practitioner. The authors emphasize that their "own personal belief concerning etiology and pathologic-physiology," as well as therapy is presented.

The section on contact dermatitis, including industrial dermatoses, is well presented, reflecting the senior author's experience in this field. Discussions of the collagen diseases, syphilis, and other conditions associated with internal disorders emphasize the cutaneous aspects of these diseases.

The type is large and clear, but the illustrations are not clear enough to identify the condition represented in most instances.

General practitioners, for whom it was written, will find the book useful. It is not intended or recommended for the dermatologist.

Raymond C. V. Robinson, M.D.

CORONARY HEART DISEASE. ANGINA PECTORIS; MYOCARDIAL INFARCTION. Milton Plotz, M.D., F.A.C.P. Pp. 353, with 107 figures and 28 tables. Indexed. Hoeber-Harper. Price $12.00.

A composite and current coverage of the most important disease of modern American medicine should be of considerable interest to the profession. Such a volume is Dr. Plotz's *Coronary Heart Disease*. It is composite and precise, and thus a broad survey of a highly complex disease is compressed into 353 quite readable pages. It is current in every respect, with all important new facets being at least mentioned and included in the bibliography. Throughout the book the author attempts to present all sides of controversial issues. In several sections his efforts to present multiple view points may lead to some confusion of those readers not well versed in this field, especially the chapters on lipid metabolism and ballistocardiography. In all fairness, however, it should be emphasized that most concepts are at least mentioned. The chapter on pathology is perhaps the least comprehensive in the entire book and, in general, those chapters dealing with the strictly clinical aspects of coronary disease are the best and are most likely to be of interest to the medical reader. Several other chapters are especially good; the brief discussion of tobacco and the heart is valuable, the section on various stress procedures is excellent, and there is a complete compilation of the disorders to be considered in differential diagnosis of coronary artery disease. Clinical management of infarction and angina are well covered in the conventional sense, and most cardiologists would accept the recommendations of Dr. Plotz save for a few minor points of controversy. There is an entire chapter on anticoagulants, and a highly sensible attitude of acceptance of these agents is adopted. A complete, though brief, review of surgical treatment and a thought-provoking chapter touching on mediolegal aspects conclude the book. Illustrations are numerous and of good quality.

In general, this book could be read with profit by all physicians whose interests have not been directly concerned with clinical cardiology and who desire to review current concepts. It is too brief and too limited to conventional clinical aspects to be of reference value to the expert in the field of atherosclerosis; it could perhaps be improved by broadening the physiologic and biochemical sections. It should be of special value to the advanced student and general practitioner, and as Dr. William Dock states in his Foreword " . . . the practicing physician and the beginner in medicine are fortunate to have such a volume as Dr. Plotz has given us."

Frank W. Davis, Jr., M.D.

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Announcement

AVAILABILITY OF SYMPOSIUM NUMBERS

Since the first publication of this JOURNAL in January, 1955, several entire issues have been devoted to Symposium numbers on topics of major interest. These Symposia are usually complete discussions, which cover conflicting points of view if necessary, which often include some original work of the several authors as well as up-to-date presentation of the literature (more current than is obtainable even in recently published textbooks), and which in general may be expected to remain scientifically valid for two or more years. The Symposia are of especial value to teachers and to medical students, as well as to practitioners.

Those so far published, with dates of publication, Guest Editors, and Symposium title, are listed here.

May, 1955	(Guest Editor, David Seegal): The Management of Patients with Primary (Essential) Hypertension. (Out of stock.)
October, 1955	(Guest Editors, Lester Breslow and Dean W. Roberts): Screening for Asymptomatic Disease. (Of special interest to public health officers and to hospital clinics.) (26 issues in stock.)
July, 1956	(Guest Editor, Louis Lasagna): Pain and Its Relief. (210 issues in stock.)
October, 1956	(Guest Editor, Robert L. Levy): Coronary Heart Disease. (45 issues in stock.)
January, 1957	(Guest Editors, David P. Earle and David Seegal): Glomerulonephritis. (105 issues in stock.)
April-May, 1957	(Guest Editor, David T. Smith): Chronic Fungus Infections. (246 issues in stock.)
June, 1957	(Guest Editor, Joseph J. Bunim): Rheumatoid Arthritis. (Published June 3.)

These several Symposium numbers, together with others to appear in future issues, may be separately purchased at $2.00 per single copy (while the supply lasts). Orders should be sent directly to the publisher, The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Missouri.